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THE NEUROLOGICAL COMPLICATIONS OF DISSECTING AORTIC ANEURYSM.

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AMONG the notable advances in medical diagnosis during the past decade one of the most striking has been the clinical recognition of spontaneous dissecting aneurysm of the aorta. Correct ante-mortem diagnosis, to-day a common event, had been made only seven times prior to 1933. Of the various clinical manifestations of the disease neurological disturbances stand high in order of importance, frequency and gravity. They were observed in approximately one-third of the cases herein reported. Since we have had the opportunity to study 38 cases of dissecting aortic aneurysm, all verified by post-mortem examination, an analysis of the neurological manifestations can be presented, together with some suggestions concerning their clinical grouping. It is anticipated that a fuller knowledge of these neurological syndromes will be of value to both the general physician and the neurologist, the former by facilitating correct diagnosis and the latter by giving order to a variety of neurological symptoms and signs.

HISTORICAL NOTE.

Laennec (1826) introduced the term "dissecting aneurysm" but it was Maunoir (1802) who first described the penetration of blood through the media of a diseased aorta. The first correct ante-mortem diagnosis, however, was made by Swaine (1855). Peacock (1843, 1863) clearly formulated the clinical syndrome as we know it to-day. The pathological anatomy found clearest expression in the writings of Erdheim (1930). Many details of the gross and microscopic pathology were added by the careful studies of Davies (1941), Sailer (1942) and others. In 1934 Shennan published his

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(5) Some cognitive factors underlying disorientation are briefly considered and their relative significance assessed. Special attention is given to impaired perception, memory retention defect and retrograde amnesia.

(6) The part played by a dominant affective attitude in provoking and maintaining disorientation is illustrated in one case. The similarity of this phenomenon to hysterical and delusional reactions is briefly considered.

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forceful penetration of blood along the media and by occlusion of the main branches of the aorta. The typical, though not invariable, clinical picture (Weiss, 1935; Glendy, Castleman and White, 1937) consists of the sudden onset of severe thoracic pain in a middle-aged individual with a previous history of hypertension. Such pain usually reaches its maximum at once, then later tends to subside. There is wide but variable radiation of the pain to the head, jaw, neck, abdomen, legs and, less frequently, the arms. Moderate collapse may occur but usually the blood-pressure is maintained. The heart is often enlarged, its rate rapid and murmurs may or may not be audible. Cardiac arrhythmia is common but auricular fibrillation rare. The temperature is usually normal but there may be a mild leucocytosis.

The remainder of the clinical picture, after the initial episode, depends entirely on the nature and extent of the dissection and the time and location of the final rupture. For example, pressure of the enlarged aorta on the œsophagus causes dysphagia; involvement of the recurrent laryngeal nerve results in hoarseness. If the cœliac axis is occluded, the clinical picture may resemble mesenteric thrombosis or other acute abdominal crises. When the renal arteries are obstructed anuria and uræmia are the consequences. Cerebral syndromes can be produced by an extension of the dissection into the carotid arteries; painful palsies of the extremities can develop through involvement of the brachial or iliac arteries, and finally, symptoms of spinal cord damage may result from implication of intercostal arteries. Thus dyspnœa, dysphagia, hoarseness, syncope, nausea, vomiting, abdominal distension, paræsthesias and paralyses may all be present on occasion. For this reason dissecting aneurysm must be differentiated from acute pericarditis, mediastinitis, pulmonary embolism, acute cholecystitis, perforation of the œsophagus, penetration of a gastric or duodenal ulcer, acute pancreatitis, coronary occlusion, mesenteric thrombosis, cerebral hæmorrhage and, as this paper will show, peripheral vascular occlusion, hæmatomyelia and various acute encephalopathies.

The most important physical signs are: (1) The maintenance of a relatively high blood-pressure in the face of a grave cardiovascular emergency (unusual in coronary thrombosis and myocardial infarction); (2) the development of a diastolic murmur and sometimes a systolic murmur heard best over the aortic area; (3) coldness and pallor or cyanosis of the arms and legs with absence of pulse. Death occurs either from infarction of a vital organ or from rupture of the dissecting blood into the pericardial, pleural or peritoneal cavities.

Helpful laboratory tests in the diagnosis of dissecting aneurysm are the

monumental work reviewing 300 cases of dissecting aneurysm. To these he was able to add 17 cases of his own. During the succeeding ten years many studies have appeared, each emphasizing special aspects of the subject.

Many cases with neurological symptoms and signs have been reported and most articles have cited, without examples, the possible neurological manifestations. Only a few isolated cases in which neurological symptoms figure prominently in the clinical picture have been published. Reitter (1916) studied a case of flaccid paraplegia resulting from a dissecting aneurysm of the aorta which occluded most of the intercostal arteries and produced infarction of the spinal cord. Kalischer (1914) reported a similar case. In one of Shennan's cases (Case 12) the aortic dissection extended into the innominate artery and, by occluding the common carotid artery, caused a left hemiplegia and hemianæsthesia. Petech (1898) reported a case in which the transverse portion of the aorta was so nearly obstructed that the brain was deprived of blood and a clinical picture of decerebrate rigidity resulted.

General Considerations.

A dissecting aneurysm is a localized dilatation of an artery due to hæmorrhage into its wall. Most of these occur in the aorta where the hæmorrhage penetrates the media, tends to encircle the vessel and traverse its entire length. It is generally agreed that disease of the media is a necessary antecedent of dissection. Such disease usually consists of hyaline, mucoid or cystic degeneration of the media without involvement of the internal elastic lamina or adventitia. Some observers consider this simply an idiopathic medial necrosis (Erdheim, 1930) while others point to the frequency of an associated hypertension and believe that medical degeneration is a secondary manifestation, analogous to benign nephrosclerosis (Sailer, 1942). Although a few cases of dissecting aneurysm have been reported without an associated intimal tear, most of them have had a rupture of the intima, usually in the ascending aorta. Frequently, the intima ruptures again at the lower extension of the dissection. The adventitia similarly is often broken through and a common mode of death is hæmorrhage into the serous cavities with the production of a hæmopericardium, hæmothorax or hæmoperitoneum. A few cases of dissecting aneurysm have occurred in conjunction with hypoplasia or coarctation of the aorta. Syphilis is not a causal factor.

The symptoms and signs of dissecting aneurysm are produced by the

105 mg. per 100 c.c. and the CO_2 combining power fell steadily. The patient died on the fifth day of illness.

Anatomical diagnosis.—Hypertensive heart disease; dissecting aortic aneurysm with infarction of the thoracic and lumbosacral spinal cord segments and the left kidney; terminal hæmopericardium.

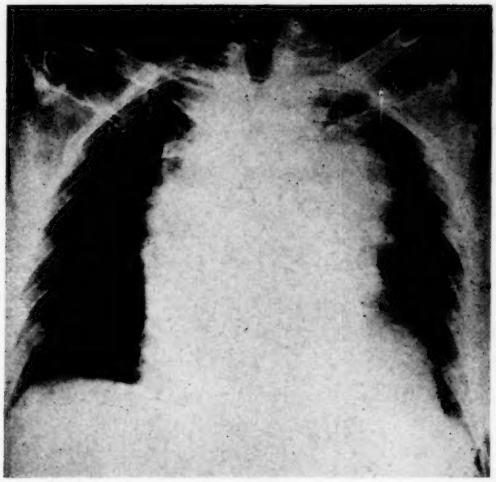

FIG. 1.—Two metre chest X-ray of Case 1. Note the increased width of the aorta and the cardiac enlargement.

Gross pathology.—The aortic dissection extended from a point immediately above the aortic valve to 2·0 cm. below the renal arteries (fig. 2). There was an intimal tear 4·0 cm. above the aortic valve. The large arteries originating at the arch of the aorta were all patent. All the intercostal arteries on both sides were shorn from the aorta by the dissecting mass of blood. The hæmorrhage extended into the wall of the left renal artery and obstructed its lumen. The aneurysm at its thickest point was about twice the normal diameter of the aorta. The lumen was reduced to about 50 per cent. of the usual diameter. The heart weighed 50 grm. and the left ventricle was hypertrophied. In the pericardial sac there was 100 c.c. of blood. The brain and upper half of the spinal cord appeared natural. Below the mid-thoracic region the spinal cord was palpably soft and on cross section the usual demarcation between grey and white matter was effaced.

Microscopic pathology.—The principal lesions were found in the lower half of the spinal cord, from the 5th thoracic through the 5th sacral segments (fig. 3). There was infarct necrosis of the anterior portions of the cord in every segment below the level of 5th thoracic. The extent of the damage varied from one segment to the next. Destruction of the anterior funiculi and the medial portions of the anterior horns was the most constant finding. Next, the anterior portions of the lateral funiculi, the intermediate column of grey matter and anterior part of the

roentgenogram of the chest which shows a greatly widened aorta with a darker central core, and the electrocardiograph which is relatively normal.

Case Material.

The 11 cases on which this report is based were all observed on the medical wards of the Boston City Hospital and were autopsied at the Mallory Institute of Pathology. Only the first two were examined by the Neurological Service. We have included only those cases in which the relation of neurological findings to the dissecting aneurysm was definite, the clinical picture clear and the examination conclusive.

Case 1.—Female, aged 68.

History.—Four hours before entry the patient experienced a sudden, excruciating, interscapular pain which penetrated the chest to the epigastrium. She was able to walk to her home, a distance of one block, and climb a flight of stairs. The pain persisted about one hour. Later her legs became weak and numb. Shortly afterwards she was brought to the hospital.

Examination.—On entry to the Neurological Service the patient was cyanotic and pulseless. The blood-pressure could not be obtained. She was conscious, alert and co-operative and was suffering with severe pain. There was a flaccid paraplegia with a loss of sensation for pain and temperature below the 8th thoracic segment. Vibration and position sense were intact. The abdominal reflexes and tendon-jerks of the legs were absent. The plantar responses were weakly extensor. Pulsations of posterior tibial and dorsalis pedis arteries were palpable and the feet were warm and of good colour. The heart was enlarged to 3 cm. beyond the mid-clavicular line. A harsh apical systolic murmur and an aortic diastolic murmur were heard. The abdomen was distended and tympanitic but peristalsis was clearly audible.

Laboratory data.—Hæmoglobin, 60 per cent.; red blood corpuscles 4·5 million per c.mm.; white blood cells, 14,500 per c.mm. Urine scanty; 30-35 red blood corpuscles and 50-60 white blood cells per high power field. Cerebrospinal fluid: pressure 220 mm.; total protein 31 mg. per 100 c.c.; colloidal gold 0001100000; 90 white blood cells, 65 per cent. polymorphonuclears per c.mm.; Wassermann and Hinton tests negative. X-ray and fluoroscopy of the chest showed a large pulsating superior mediastinal mass displacing the trachea posteriorly and to the left (fig. 1).

Course.—The patient was given circulatory stimulants and within a few hours temperature was 100·5°F., pulse 88, respirations 25 and blood-pressure in the arms 140/80 mm. There was a pulsus alternans. The pain continued but was partially relieved by codeine. At first it was thought that the patient was in urinary retention but catheterization revealed no urine in the bladder.

The next day, the second day of illness, the patient was somewat confused and less responsive. Respirations were more rapid and deeper. The level of sensory loss had risen to D5 on the right side and D6 on the left. Light touch, position and vibratory sense were impaired but not lost in the legs. The left patellar-jerk was elicited but not the right one or either ankle-jerk. She was incontinent of fæces. Her arms were strong and movements well co-ordinated.

During the third, fourth, and fifth days of the illness the patient excreted less than 150 c.c. of urine. Non-protein nitrogen rose from 50 mg. per 100 c.c. to

posterior funiculi were involved (figs. 4 and 5). At some levels the softening included the posterior half of the lateral funiculi, thus interrupting the cortico-spinal tracts. The posterior horns of grey matter and the posterior funiculi were spared for the most part throughout the cord.

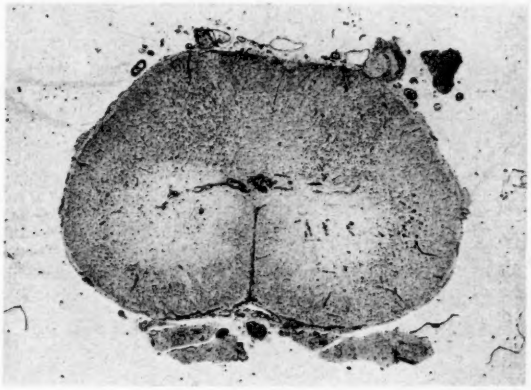

FIG. 5.—Section of 5th lumbar segment corresponding to fig. 4. (Loyez stain funiculi and anterior horns. (Cresyl violet stain.)

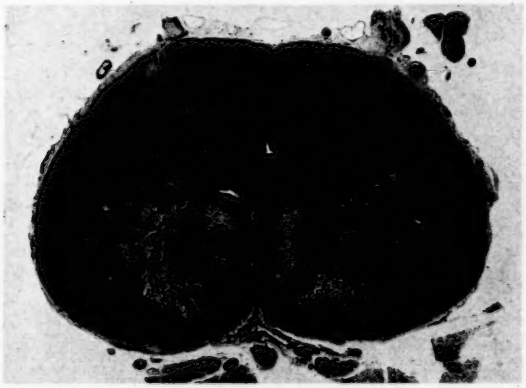

FIG. 4.—Section of the 5th lumbar segment showing ischæmic necrosis of anterior for myelin.)

In routine cell stains the softened tissue appeared to be œdematous. Astrocytes and oligodendrocytes either had disappeared entirely or remained as shrunken cell fragments with pyknotic nuclei. Many polymorphonuclear leucocytes had migrated into the perivascular spaces and into the necrotic tissue; endothelial and microglial

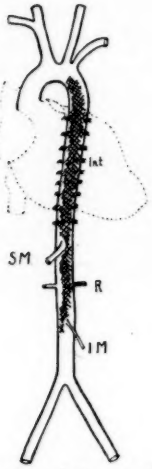

FIG. 2.—Diagram to show the extent of the aortic dissection (indicated by cross hatching) Case 1.

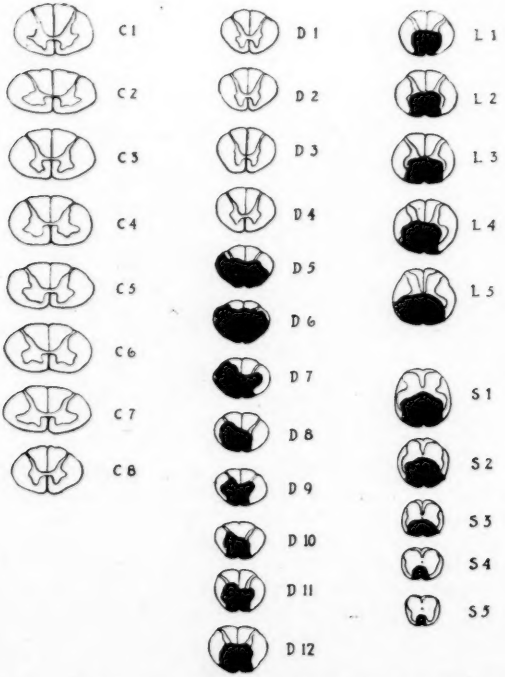

FIG. 3.—The extent of the spinal cord damage is shown in black (Case 1).

were not involved. The right renal artery was also obstructed. The dissection extended as far as the bifurcation but no other important arterial trunks were significantly narrowed (fig. 6).

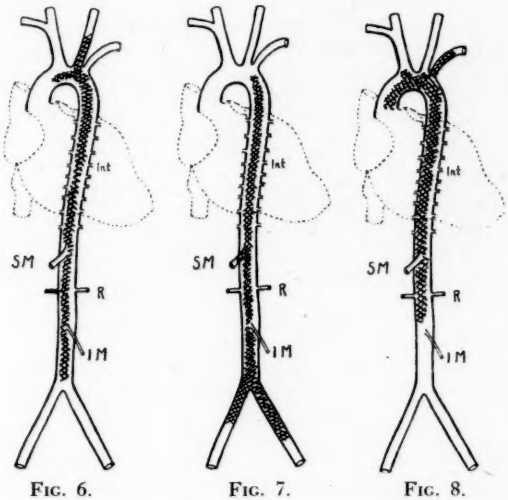

FIG. 6. FIG. 7. FIG. 8.

FIG. 6 (*Case 2*).—Diagram to show the extent of aortic dissection.
FIG. 7 (*Case 3*).—Diagram to show the extent of aortic dissection.
FIG. 8 (*Case 7*).—Diagram to show the extent of aortic dissection.

The cerebral vessels were natural in appearance. The left posterior communicating and the anterior communicating arteries were very small. The only perceptible change in the brain was slight swelling and softening of the left frontal, parietal and temporal lobes. Here the usually clear demarcation between grey and white matter was obliterated.

Microscopic examination of sections of the left frontal lobe, stained with cresyl violet, showed pyknosis and shrinkage of nerve cells and glia in the cerebral cortex. The oligodendrocytes were swollen. Polymorphonuclear cells had migrated into necrotic brain and leptomeninges. The endothelial cells of capillaries and veins had increased in number and size. No changes of this type were demonstrable in the right cerebral hemisphere.

Comment.—The first mental symptoms in this case were those commonly seen in a toxic psychosis from any cause. With the development of coma, however, it became evident that some grave disorder of cerebral function had occurred. This was clarified when autopsy disclosed that the left common carotid artery was occluded and that the anterior half of the left cerebral hemisphere, the parts supplied by the anterior

cells were increased in number and size. Most of the anterior horn cells had disappeared and some of them had been replaced by microglial cells. Other nerve cells remained as pale staining "shadows" or as shrunken, darkly stained remnants. A few cells had rounded contours and had undergone central chromatolysis.

The arteries of the spinal cord had slightly thickened walls, some of which were hyalinized. There was no definite intimal hyperplasia. Small numbers of lymphocytes were present in the perivascular spaces.

The myelin sheaths were degenerated in the affected portions of the cord (fig. 4). Some nerve fibres were greatly swollen, giving a cribriform appearance to the tissue. There were no products of degenerating myelin in microglial cells and no free fat in the tissues.

Comment.—The sphincter incontinence, the paralysis and loss of pain and temperature sensation below the 5th thoracic segment were caused by interruption of the corticospinal and lateral spinothalamic tracts. The preservation of light touch, vibratory and postural sensibility were due to the relative sparing of the posterior columns. It should be noted that all the intercostal arteries were occluded. The microscopic findings were compatible with an infarct of five days' duration.

Case 2.—Male, aged 32.

History.—Two hours before entry the patient suddenly experienced a severe pain in the lower thoracic region which radiated to the epigastrium. This was followed within a few minutes by dyspnœa, vomiting and cyanosis. The patient was known to have had arterial hypertension for the past six years.

Examination.—Temperature 98·6° F.; pulse 116; respirations 30; blood-pressure 180/60. The patient appeared to be in great pain. He was oriented and rational. The heart was enlarged to just beyond the left mid-clavicular line. Rate and rhythm were normal. Motor power in the extremities was good and no sensory defect could be detected. The colour and temperature of the skin and pulsations of peripheral arteries of the extremities were normal.

Laboratory data.—White blood-count 29,500 per c.mm. Blood Wassermann and Hinton tests were negative. Non-protein nitrogen 26 mg. per 100 c.c. Electrocardiogram showed no abnormalities.

Course.—On the sixth hospital day the patient became excited and struck a nurse without provocation. He expressed a desire to kill himself. Mental examination at this time disclosed an inability to speak coherently, confusion, perseveration of words and thought and mood alterations which varied from melancholia to euphoria. He was incontinent of urine. The psychiatrist summarized these findings as "emotional and intellectual deterioration." These psychic abnormalities remained and on the eighth day of his illness he became dyspnœic, cyanotic, and passed into coma. Blood-pressure at this time was 100/40. He died on the ninth day of illness without regaining consciousness. The clinical record made no reference to reflex changes or paralysis.

Anatomical diagnosis.—Dissecting aortic aneurysm with obstruction of the left common carotid and right renal arteries. Recent infarction of the left frontal, temporal and parietal lobes and of the right kidney.

The dissection began at the arch or transverse portion of the aorta and extended into the left common carotid artery, almost if not completely occluding it. The descending thoracic aorta was widened by the dissection, but the intercostal arteries

Case 4.—Female, aged 42.

History.—The patient suddenly developed severe pain in her chest and epigastrium three hours before entry to the hospital. The pain radiated into the abdomen. The left leg became weak and numb at about the same time. She had received specific therapy for latent syphilis for the past seven years.

Examination.—Temperature 98·6° F.; pulse 116; respirations 30; blood-pressure 140/80, right arm and 160/70, left arm. The patient was suffering such intense pain that she took little notice of what was happening about her. However, she was conscious. The heart was enlarged to the left; cardiac rhythm was regular and no murmurs were heard. Both arms could be moved but the left leg was paralysed. No arterial pulsations could be felt in the left leg and the skin was cold and cyanotic. The left patellar and ankle reflexes were absent.

Laboratory data.—White blood cells 7,000 per c.mm. Urine: 10-15 white blood cells per high power field. Non-protein nitrogen 67 mg. per 100 c.c. The blood Kahn and Hinton tests were positive. The electrocardiogram was normal.

Course.—Death occurred on the third day of the illness.

Anatomical diagnosis.—Dissecting aneurysm of the aorta with extension into the innominate, the right subclavian and common carotid, the superior mesenteric, left renal and both iliac arteries. Hypertensive heart disease; malignant nephrosclerosis.

There was dissection of the aorta from 1·5 cm. above the aortic ring to the iliac arteries. Although the lumen of the innominate, right common carotid and subclavian arteries were reduced to a considerable degree, they were not occluded. The dissection had extended into and completely obliterated the lumen of the left iliac artery. The peripheral nerves and spinal cord were not examined microscopically. There was no evidence of syphilitic aortitis or neurosyphilis.

Comment.—The blood supply to the right arm and right cerebral hemisphere was not reduced to a significant degree in this case nor were the intercostal arteries implicated. The only neurological signs were those caused by an ischæmic necrosis of the peripheral nerves in the left leg.

Case 5.—Male, aged 54.

History.—About two hours before admission to the hospital the patient suddenly experienced a severe pain of a sharp oppressive nature in the interscapular region. The pain did not radiate and after half an hour diminished in intensity. While the patient was sitting down sipping water he noticed that his left leg below the knee had become numb. Shortly afterwards the left leg became weak and about an hour later the right leg was similarly affected with weakness and numbness. He vomited once and had a constant desire to defæcate.

Examination.—Temperature 98·8°F.; pulse 100; respirations 30; blood-pressure 200/100 in the right arm and 205/100 in the left arm. The patient was alert and responsive. The heart was slightly enlarged to the left but no murmurs were heard. The skin over the lower abdomen and both legs was cold and of a mottled violaceous colour. Arterial pulsations in the legs were not palpable and blood-pressure in the legs could not be recorded. All movements of the legs were weak, the left more so than the right. Pain and light touch sensation were absent below an indefinite line just below the knee on the lateral aspect and above the knee on the medial aspect of the legs. The left patellar and ankle-jerks were absent, but those on the right were still present. Plantar reflexes were absent and abdominal reflexes were present. Vibratory and position sense were absent in feet and ankles.

and middle cerebral arteries, had undergone recent infarct necrosis. The microscopic findings were of the type usually seen in an infarct of twenty-four to forty-eight hours' duration. It should have been possible to demonstrate a right hemiplegia and reflex changes. Probably the inadequacy of the anterior and posterior communicating arteries of the circle of Willis permitted such widespread cerebral damage from occlusion of the common carotid artery.

Case 3.—Male, aged 62.

History.—One and a half hours before admission to the hospital the patient experienced a severe pain in the left chest. In the next half-hour it radiated into both arms, thence into the abdomen, the penis, and down both legs. Just before admission both legs became paralysed. He had a sense of fullness in the suprapubic region and a constant desire to micturate. For the past two years the patient had had attacks of substernal pain after exertion which were diagnosed as angina pectoris.

Examination.—Temperature 98·6° F.; pulse 54; respirations 20; blood-pressure 250/95. The patient was conscious and able to relate the details of his illness. The heart was not significantly enlarged. There were occasional dropped beats. A rough systolic murmur was heard at the apex. Both legs were paralysed, pulseless, cold and cyanotic. The tendon-jerks could not be elicited in either leg. There was no mention of cutaneous sensory impairment.

Laboratory data.—White blood-count 14,600. Urine sediment contained 25 red blood corpuscles and 2-3 white blood cells per high power field. Blood Hinton test was negative. Non-protein nitrogen was 40 mg. per 100 c.c.

Course.—Nine hours after entry the blood-pressure had fallen to 105/80 in each arm. Abdominal distension became marked. Medical shock supervened. The patient lapsed into coma and died fourteen hours after onset of his illness.

Anatomical diagnosis.—Dissecting aortic aneurysm with occlusion of the cœliac axis superior mesenteric artery and both iliac arteries; recent infarction of the large and small intestine; gangrene and ischæmic neuropathy of both legs; terminal hæmorrhage into retroperitoneal tissues. Hypertensive and coronary heart disease.

The dissection was massive; it extended from the origin of the left subclavian artery to a point 20 cm. down the left iliac and 10 cm. down the right iliac arteries. A few of the intercostal arteries were obstructed but most of them escaped, as did the renal and inferior mesenteric arteries (fig. 7). The entire small intestine and all the colon except the sigmoid were infarcted. A retroperitoneal blood clot measured 15 by 15 by 2 cm. and could be traced to a rupture of the dissection through the adventitia of the left iliac artery. No definite gross or microscopic changes could be detected in the spinal cord or peripheral nerves.

Comment.—The clinical and neurological signs were consistent with ischæmic necrosis of the peripheral nerves and gangrene of the legs. This was due to occlusion of the iliac arteries. The intercostal arteries were not interrupted in sufficient number to interfere with the circulation of the spinal cord. The patient did not survive long enough for demonstrable microscopic changes to develop.

Laboratory data.—White blood cells 11,000. Urine: 2-3 red blood corpuscles per high power field. Non-protein nitrogen 21 mg. per 100 c.c. The electrocardiogram was interpreted as showing "myocardial disease." The spinal fluid showed no abnormality.

Course.—The interscapular pain recurred about twelve hours after the onset of the illness and radiated anteriorly. The patient had a generalized convulsion and then expired one hour later.

Anatomical diagnosis.—Dissecting aortic aneurysm with obstruction of the left renal and both iliac arteries; ischæmic neuropathy and gangrene of both legs; recent infarction of the left kidney; terminal rupture into the mediastinum and left pleural cavity. Hypertensive and arteriosclerotic heart disease. Early alcoholic cirrhosis.

The dissection extended from just beyond the origin of the left subclavian artery down the left side of the aorta into the left renal and left iliac arteries and, to a lesser extent, the right iliac artery. At one point the dissection had penetrated the adventitia of the descending thoracic aorta filling the mediastinum and left pleural cavity with blood. All other branches of the aorta remained patent. The left kidney and both legs were deprived of blood.

No microscopic examination of the peripheral nerves was made. There were no significant changes in the cerebrum or brain-stem.

Comment.—The terminal convulsion was probably the result of cerebral ischæmia incident to the massive hæmorrhage into the mediastinum and the left pleural cavity, since none of the major arteries to the brain were involved by the dissecting aneurysm. Again, the clinical symptoms of sensory loss, paralysis and inadequate peripheral circulation were found to be caused by occlusion of the iliac arteries.

Case 6.—Male, aged 58.

History.—The patient was well until two hours before entry to the hospital. At that time he experienced a severe pain in the right jaw which rapidly spread to the neck, right arm and leg, posterior chest and abdomen. Shortly afterwards the right leg became paralysed, numb and cold.

Examination.—Temperature 98°F.; pulse 100; respirations 25; blood-pressure 88/68 in the right arm and 192/108 in the left arm. The patient was conscious and rational and in obvious discomfort. The arterial pulsations were much reduced in the right arm. The right popliteal, posterior tibial and dorsalis pedis arteries did not pulsate. Coolness and mottled cyanosis of the right foot and leg were noted. Only feeble movements were possible with the right foot and leg and the patellar and ankle-jerks and plantar response were absent. The sensory deficit was not clearly described. Movements and sensation in the right arm were unimpaired.

Course.—The pain was lessened by morphine. The patient was found dead in bed the morning after entry, less than twenty-four hours after the beginning of the illness.

Anatomical diagnosis.—Dissecting aortic aneurysm with partial occlusion of the innominate and right subclavian arteries and complete occlusion of the right iliac and femoral arteries; terminal hæmopericardium with cardiac tamponade. Hypertensive heart disease.

There was a tear in the intima about 4·0 cm. above the aortic ring and from this point dissection extended downwards into the pericardium and upwards into

the innominate, then throughout the length of the aorta, on the right side, into the right iliac and femoral arteries for a distance of 8·0 cm. Only the iliac artery was occluded.

No gross or microscopic abnormalities of the brain were noted. The peripheral nerves were not examined microscopically.

Comment.—The pain radiated along the course of the partly obstructed right common carotid and subclavian arteries. This probably indicated the site of the first dissection. Neither the brain nor the right arm suffered sufficient reduction of blood supply to produce symptoms. It is interesting that the dissection remained on the right side of the aorta throughout its course, thus causing only right-sided signs.

Case 7.—Male, aged 62.

History.—The patient entered the hospital a few hours after noticing numbness, weakness and finally paralysis of the left arm. Soon he became generally weak and ill and went to bed. He awakened shortly with severe left upper quadrant pain which radiated into the lumbar region.

Two years previously he had suffered a "shock" or "stroke" which left him with a slight left hemiparesis.

Examination.—Temperature 100°F.; pulse 80; respirations 26; blood-pressure 100/70 (arm not stated). The left arm was cold and the left radial pulse was absent. The left hand grip was feeble and movements of the forearm were weak. There was no mention of sensory loss in the record. The left supinator reflex was absent and the left biceps and triceps reflexes were less active than those on the right. The tendon reflexes in the legs were approximately equal and the left plantar response was extensor.

Course.—The patient suffered a great deal of pain and required large amounts of morphine for relief. He became increasingly restless and died during the night less than twenty-four hours after the onset of his illness.

Anatomical diagnosis.—Dissecting aneurysm of the aorta with partial occlusion left subclavian artery; ischæmic necrosis of nerves of the left arm; terminal hæmorrhage into superior mediastinum and left pleural cavity. Hypertensive heart disease; benign nephrosclerosis; cerebral atherosclerosis and encephalomalacia with old infarction of right internal capsule.

The dissection in this case extended from the root of the aorta to the origin of the renal arteries. Although it extended into the innominate, left common carotid and subclavian arteries, only the latter was occluded. Most of the intercostal arteries escaped (fig. 8). At one point the dissection ruptured through the adventitia of the aorta and filled the superior mediastinum and left pleural cavity with blood. The heart was enlarged and the left ventricle hypertrophied. The cerebral arteries were moderately atherosclerotic. The right internal capsule and lenticular nucleus were partly destroyed and a cavity surrounded by grey, firm tissue replaced them. The nerves of the left arm were not examined.

Comment.—This is an example of ischæmic neuropathy of the left arm. The relative infrequency with which this lesion appears in comparison to ischæmic neuropathy of the legs is probably due to the extensive collateral circulation about the shoulder. The left Babinski sign was obviously related to the old cerebral infarction. An unusual feature of

this case was the painless onset of weakness, numbness and coldness of the left arm. Even though the dissection extended into the innominate and left common carotid arteries it did not sufficiently reduce their calibre to cause symptoms of cerebral ischæmia.

Case 8.—Male, aged 66.

History.—While walking on the street the patient experienced numbness, weakness and coldness of the right leg. He walked to his home with difficulty. Within a few minutes he noted pain and cramping sensations in the left leg. This leg also became weak and numb. The patient became short of breath, weak, and just before entry to the hospital developed a severe epigastric pain. Two to three years before entry the patient had had a shock ("stroke") from which he recovered with only a slight residual weakness of the left side of the body.

Examination.—Temperature 97·6°F.; pulse 100; respirations 22; blood-pressure 90/60. The patient was apprehensive and in a state of shock. The right leg was cold and of mottled bluish colour. No pulse could be palpated in the right leg and only the femoral pulse was present in the left one. The right leg was flaccid, paralysed, anæsthetic, and arreflexic. The left leg was weak but tendon reflexes were obtainable.

Laboratory data.—No urine excreted. White blood-count 20,000. Blood Hinton negative.

Course.—The weakness of the left leg gave way to flaccid paralysis one hour after admission. The mottled discoloration and coldness spread to the left leg and lower abdomen. The level of anæsthesia reached the umbilicus. The patient became extremely dyspnœic, the abdominal pain increased, the blood-pressure fell and death occurred six hours after entry to the hospital.

Anatomical diagnosis.—Dissecting aortic aneurysm with occlusion of the right renal and both iliac arteries; ischæmic neuropathy of both legs and, query, ischæmic myelopathy; recent infarction of right kidney. Arteriosclerotic heart disease; benign nephrosclerosis; cerebral atherosclerosis and encephalomalacia.

The dissection began at a point below the left subclavian artery and extended to the iliac arteries. Involvement of the intercostal arteries was not recorded. The dissection penetrated the adventitia of the thoracic aorta with a resulting massive left hæmothorax. The aorta was markedly atherosclerotic. The only pathological changes in the brain were those resulting from atherosclerotic occlusion of several small cerebral arteries. Microscopic sections of the lumbosacral spinal cord revealed no abnormalities. The peripheral nerves were not examined.

Comment.—It was difficult to decide in this case whether the neurological symptoms were due to ischæmic necrosis of peripheral nerves or the spinal cord. The weakness and numbness of the distal parts of each leg in conjunction with peripheral circulatory obstruction indicated an occlusion of the iliac arteries. The ascension of the sensory level to the 10th thoracic dermatome suggested damage to the spinal cord. Unfortunately the adequacy of the intercostal arteries was not carefully tested. The absence of histological changes in the spinal cord six hours after interference with the blood supply does not exclude the possibility.

Case 9.—Male, aged 59.

History.—Three hours before admission the patient suffered a severe interscapular pain which radiated into the lower back and both legs. At the same time his legs became so weak that walking was impossible.

Examination.—Temperature 98°F.; pulse 100; respirations 27; blood-pressure 120/80. The patient was in full possession of his mental faculties. The heart was enlarged 3 cm. beyond the left mid-clavicular line. The legs were mottled white and blue in colour and were cold. Both legs were weak and reflexes were absent. There was no record of sensory disturbances.

Course.—The pain continued and the patient became increasingly restless. On the second hospital day he suddenly became cyanotic and dyspnœic, with moist rales throughout both lung fields. He died a few hours later, on the second day of his illness.

Anatomical diagnosis.—Dissecting aortic aneurysm with occlusion of both iliac arteries, thrombosis of the abdominal aorta; ischæmic neuropathy and gangrene of both legs; terminal mediastinal hæmorrhage. Hypertensive heart disease.

The dissection of the aorta began 10 cm. above the aortic ring and extended to the bifurcation. None of the major trunks were obstructed. Two thrombi which almost completely occluded the aorta were found 17 cm. and 4 cm. above the bifurcation. Most of the dissection was along the left margin of the thoracic aorta so that the intercostals escaped damage. A tear in the adventitia of the thoracic aorta permitted escape of blood into the mediastinum. The heart was enlarged and the left ventricle hypertrophied. The spinal cord and nerves were not examined microscopically.

Comment.—The iliac arteries were not occluded by extension of the blood into the media. Rather, a thrombus had formed in the abdominal aorta, thus preventing blood from circulating into the legs. The clinical picture was one of ischæmic paralysis.

Case 10.—Male, aged 47.

History.—Five hours before entry to the hospital the patient developed a severe substernal pain which radiated to the right scapula then downwards into the right leg. Following this the leg became cold and weak and would no longer support him. He had had hypertension for four years.

Examination.—Temperature 96·8°F.; pulse 68; respirations 16; blood-pressure 115/60 in right arm, 145/60 in left arm; 160/60 in left leg and 0 in the right leg. He was oriented and rational. The left border of the heart was at the anterior axillary line. The right leg was cold, pale and paralysed. The right patellar and ankle-jerks, as well as the plantar responses, were absent. All forms of sensation were impaired or lost below the right mid-thigh.

Course.—The pain failed to abate and despite circulatory stimulants the patient went into shock and died less than twelve hours after entry to the hospital.

Anatomical diagnosis.—Dissecting aortic aneurysm with occlusion of the right iliac and femoral arteries; ischæmic neuropathy; hæmopericardium and cardiac tamponade. Hypertensive heart disease.

The dissection extended from the aortic ring into the right iliac artery. For the most part it was on the right side of the aorta, thus sparing all the important branches. Near the aortic ring the aneurysm ruptured into the pericardial sac, filling it with blood and causing death by cardiac tamponade. No neuropathological examination was made.

Comment.—The only parts of the nervous system deprived of blood were the peripheral nerves of the right leg.

Case 11.—Male, aged 54.

History.—While at work the patient suddenly developed a severe epigastric pain. Soon afterwards the left leg became painful, cold, numb and weak.

Examination.—Temperature 90°F.; pulse 80; respirations 22; blood-pressure 170/64. The patient was conscious. Except for the weakness and subjective numbness of the left leg no neurological findings were recorded.

Course.—The patient went into a state of shock and died in a few hours after entry to the hospital, or twenty-three hours after the onset of his illness.

Anatomical diagnosis.—Dissecting aortic aneurysm with occlusion of the left iliac artery.

The dissection extended from the arch of the aorta to the bifurcation. The innominate, left common carotid, superior and inferior mesenteric arteries were narrowed but not occluded. The dissection ruptured through the intima into the lumen of the left iliac artery. The spinal cord and nerves were not examined.

Discussion.

Very little information as to the incidence of neurological disturbances in dissecting aneurysm is available. Because of the catastrophic nature of the illness many patients afflicted with this disease cannot undergo complete neurological examination. Further, competent neurologists rarely have access to these cases since most of them are treated on medical wards. For these reasons detailed evaluation of nervous function is seldom obtained. Of the 300 cases which Shennan collected and analysed, 45 had some neurological complication but, judging from our data, the actual incidence of nervous disorder should be higher. In the past ten years, 38 cases of dissecting aortic aneurysm have been autopsied at the Boston City Hospital. 30 per cent. of these cases presented neurological symptoms due unmistakably to the dissection. In this group there were 9 cases of ischæmic neuropathy, 1 of encephalopathy and 1 of myelopathy. In Case 8 cord disease may have existed as well as disease of the peripheral nerves, despite a negative microscopic examination.

The correct ante-mortem diagnosis was made in 55 per cent. (20) of the 38 cases. However, over 80 per cent. of the cases with neurological symptoms were correctly diagnosed before death while this was true of only 44 per cent. of the cases without neurological findings. It would seem that the presence of neurological disorders almost doubles the likelihood of correct ante-mortem diagnosis of dissecting aortic aneurysm.

The average age of the eleven cases with neurological symptoms was 55 years and 9 of the 11 cases occurred in males. Hypertension and hypertensive heart disease as indicated by increased size of the heart and hyper-

trophy of the left ventricle invariably preceded the aortic dissection. At the time of entry to the hospital the blood-pressure was over 200 in only 2 of the cases, however, and in half of them it was within normal limits. A rather frequent finding was a moderately elevated systolic and a low diastolic blood-pressure.

The duration of illness in our cases varied from six hours to nine days and averaged thirty-six to forty-eight hours. This figure is not significantly different from those without involvement of the nervous system. In fact, the 2 cases with the most extensive involvement of the brain and spinal cord survived longer than those with only peripheral nerve disease.

There were certain points of interest in the general symptomatology. In all except 2 cases the first symptom of aortic dissection was pain. It was of sudden onset and described as tearing, piercing, or aching. It varied in intensity from a mild, tolerable ache to a pain of agonizing severity. The location of the pain depended on the site of dissection. Since most of the aneurysms began in the thoracic aorta the pain was usually in the chest, either substernal or interscapular. In one case it was localized to the left upper quadrant; in another it was felt in the epigastrium and in a third in the jaw and right side of the neck. Radiation of the pain in the direction of the dissection or into a field supplied by an occluded artery was frequent. Symptoms of peripheral circulatory insufficiency in a limb preceded pain in 2 cases. Some patients, in addition to pain, had an alarming sensation of something tearing or giving way in the chest. Weakness and faintness were common but loss of consciousness at the time of onset did not occur in our cases.

The neurological complications of dissecting aortic aneurysm are produced by interference with the blood supply of the central or peripheral nervous system. On the basis of the region affected they naturally fall into three groups.

I.—Ischæmic Necrosis of the Peripheral Nerves. (Pulseless cold extremity with weakness, anæsthesia and loss of tendon reflexes.)

II.—Ischæmic Necrosis of the Spinal Cord. (Flaccid paralysis, urinary retention and anæsthesia below a level on the trunk.)

III.—Ischæmic Necrosis of the Brain. (Confusion, stupor or coma with flaccid hemiplegia, hemianæsthesia and aphasia.)

There are three ways in which branches of the aorta may be obstructed by a dissecting aneurysm.

(1) The aortic dissection may extend into the branch thus occluding the lumen. This was the mechanism in Cases 2, 3, 4, 5, 6, 7, 8, 10, 11.

(2) The dissection may narrow the aorta or one of the branches and cause thrombosis. This happened in Case 9.

(3) The dissection may shear or sever small branches from the main trunk of the aorta as was observed in Case 1.

The number and size of anastomotic vessels are important factors in determining whether ischæmic necrosis will occur.

Ischæmic Necrosis of the Spinal Cord.

Myelomalacia on the basis of dissecting aneurysm is a rare syndrome. Although the diagnosis has occasionally been made, only two cases (Reitter, 1916; Kalischer, 1914) have previously been studied pathologically. Our case, the third to be reported, offered a unique opportunity to re-evaluate the blood supply of the spinal cord in the light of the pathological findings.

The upper half of the spinal cord receives most of its blood supply from the vertebral arteries and only a small amount from branches of the ascending and deep cervical and costovertebral arteries. The lower half of the spinal cord depends almost entirely on branches of the intercostal, lumbar, iliolumbar and lateral sacral arteries (Suh and Alexander, 1939). Each spinal artery divides into three branches, two of which supply ligamentous structures and a third, the lateral spinal artery, which supplies the spinal cord and meninges. The lateral spinal artery accompanies the appropriate spinal nerves and, after penetrating the dura with the nerves, divides into anterior and posterior branches which continue along with the corresponding nerve roots. Kadyi (1889), however, pointed out that only about a quarter of the nerve roots in man are accompanied by segmental arteries recognizable by the unaided eye. In the average individual there are 6 to 8 anterior radicular arteries, the largest of which is in the upper lumbar region (a. radicalis anterior magna) and 5 to 8 posterior radicular arteries.

The anterior radicular arteries are considerably larger than the posterior radicular arteries and contribute most to the spinal cord circulation. The segmental arteries are neither symmetrically distributed nor uniform in size. The largest vessel is in the upper lumbar region and occurs as an unpaired structure. Tanon (1908) injected the spinal cord at various levels through the segmental arteries and discovered that the entire cord could be injected from the lumbar arteries but that in the thoracic region above D9, injections from any segmental branch could be made only into very small stretches.

The segmental character of spinal circulation is reinforced by the development of intersegmental anastomoses through ascending and descending branches of adjacent radicular arteries. Three primary chains

are thus formed: a single anterior spinal artery which extends the length of the cord and a pair of posterior spinal arteries situated near the entrance of the dorsal roots. From these primary chains are derived the pial vascular network and the penetrating arteries of the spinal cord (Tureen, 1938).

The anterior radicular arteries with the anterior spinal artery and its sulcal branches (Herren and Alexander, 1939) supply the anterior horns, the central grey, the lateral horns, Clarke's columns and the anterior and lateral funiculi, including the pyramidal system. The posterior radicular arteries and the posterior spinal arteries supply the posterior columns and the posterior horns (Winkler, 1918).

Several important clinical implications result from the preceding anatomical analysis. First, the integrity of the spinal cord circulation depends on a relatively small number of segmental arteries. Second, the largest contribution to the lower thoracic and lumbosacral cord is from a single unpaired lumbar artery rather than from the vertebrals. Third, the anterior spinal artery, instead of being a single vessel, arising from the vertebrals, passing down the anterior sulcus and receiving a few insignificant contributions from the segmental arteries, actually is merely a secondary fusion of adjacent branches of the radicular arteries. Fourth, the upper and mid-thoracic region of the cord has a meagre segmental supply and thus is the area most subject to vascular embarrassment. Finally, it is evident that arterial occlusion at one level can produce widespread myelomalacia at a considerable distance from the involved vessel.

The occurrence of myelomalacia from occlusion of the intercostal arteries or from aortic obstruction has been a matter of some dispute. Kahler (1934) and Rogers (1939) expressed the opinion that occlusion of the abdominal and thoracic aorta would not affect the spinal cord because of the rich collateral circulation. Kahler cited several human cases of aortic occlusion in which the spinal cord was normal. Experimental ligation of the aorta failed to clarify the matter because the animals died of gangrene of the legs before sufficient time elapsed for histological changes to occur in the spinal cord. Tureen (1938) found, however, that if the aorta were clamped off for varying periods of time up to several hours, alterations of the anterior horn cells appeared within twenty-four to thirty-six hours.

Our case and similar ones should remove any doubt that sudden occlusion of all the intercostal arteries will result in ischæmic infarction of the lower thoracic and the lumbosacral portions of the spinal cord. In the

cases of dissecting aneurysm in which the spinal cord was spared we found that few or none of the intercostal arteries were implicated.

The microscopic pathology of the spinal cord in our Case 1 and that reported by Reitter were identical. In each the histological changes resembled those which have been described in thrombosis of the anterior spinal artery. The myelinated nerve fibres and supporting tissue in the anterior and lateral funiculi, and the nerve cells in the anterior and lateral horns had undergone ischæmic necrosis. The posterior horns and posterior funiculi remained intact apparently because the collateral blood supply here was more abundant than within the zone supplied by the anterior spinal artery.

Dissecting aortic aneurysm with ischæmic necrosis of the spinal cord must be differentiated clinically from spinal epidural abscess and carcinoma, spontaneous hæmatomyelia, thrombosis of the anterior spinal artery and acute myelitis. All are alike in causing the clinical picture of an acute transverse lesion of the cord. In spontaneous hæmatomyelia there is usually severe pain in the region of the vertebral column followed by flaccid paralysis and sensory loss below the level of the lesion. Pain and temperature sensation are impaired more than touch, vibratory and position sense. In some cases there may be a small amount of blood in the cerebrospinal fluid. This condition can be distinguished from dissecting aneurysm by a roentgenogram of the chest which will demonstrate a greatly widened thoracic aorta in the latter. Thrombosis of the anterior spinal artery, usually caused by syphilitic endarteritis and rarely by other vascular diseases, may resemble the myelomalacia of dissecting aortic aneurysm, though as a rule, pain is mild or absent and signs of hypertensive cardiovascular disease will not be present. Spinal epidural abscess or cancer may cause pain in or about the vertebral column followed in a short time by paraplegia, anæsthesia, and disturbance of bladder and rectal functions. The finding of a dynamic block by lumbar puncture, destruction of vertebræ by X-ray and pain and tenderness at the site of the affected vertebra, should assist in the differential diagnosis.

It may at times be difficult to distinguish between dissecting aortic aneurysm with myelomalacia and the condition known as acute infectious myelitis. The latter is of acute onset with paraplegia, sensory loss below a level on the trunk, paralysis of bowel and bladder functions and occasionally with severe pains of radicular character. Unlike the myelomalacia of dissecting aortic aneurysm there is usually pleocytosis and elevation of the cerebrospinal fluid protein. Other rarer types of myelitis may offer diagnostic difficulty. From the practical point of view widen-

ing of the aorta in an X-ray of the chest will confirm the diagnosis of dissecting aortic aneurysm in most cases.

Ischæmic Necrosis of Nerves.

This was by far the commonest neurological complication of dissecting aortic aneurysm, occurring three times as often in our cases as involvement of the spinal cord and brain. The symptoms of ischæmic neuropathy appeared suddenly in all cases and reached their maximum intensity within a few minutes to hours. In most but not all of the cases the first symptom was severe pain referred distally into the extremity, not following the distribution of nerve trunks. Numbness, coldness and tingling were the first symptoms in two of the cases and sooner or later were present in all. Loss of muscular power amounting in some instances to paralysis was a rare initial complaint. Often, however, weakness of a limb is masked by pain and paræsthesias and so may be confused with a natural tendency to immobilize a painful extremity.

The mechanism of peripheral nerve damage in the course of arterial disease is still unsettled. Ischæmic neuropathy has been described in many diseases (Fetterman and Spitler, 1940) but the pathological evidence has not usually been conclusive. Nevertheless, recent clinical and experimental investigation of the effects of vascular obstruction on peripheral nerves have clarified several aspects of the problem (Wortis, Stein and Jelliffe, 1942; Denny-Brown and Brenner, 1944).

The blood supply of nerves, like that of the spinal cord, is fundamentally regional (Adams, 1942). Each nerve receives several nutrient branches from the nearest arterial trunk. Each nutrient artery to a nerve supplies a specific region and ascending and descending branches of these nutrient arteries make abundant anastomoses with adjacent vessels. This collateral circulation is so rich that the occlusion of any one or several nutrient arteries usually has no effect on the nerve. Ischæmic necrosis is possible only if the main artery to a limb is obstructed or if many of the fine arterial branches within the substance of a nerve become occluded. An example of the latter is thromboangiitis obliterans (Goldsmith and Brown, 1935); of the former, dissecting aortic aneurysm.

The peripheral nerves from cases of ischæmic paralysis were not examined in any of our cases. Presumably they would show an ischæmic necrosis just as the other involved nervous tissue did.

Ischæmic Necrosis of the Brain.

Because the circle of Willis usually insures adequate blood supply to the brain even though one of the carotid or vertebral arteries is occluded

ischæmic necrosis of the brain is less common than either peripheral nerve or spinal cord complications.

The clinical picture which follows upon dissecting aortic aneurysm with occlusion of the internal carotid artery has a fairly definite pattern, though subject to minor variations. The chest pain is followed by an alteration of consciousness with blindness and retinal changes in one eye and flaccid hemiplegia and hemianæsthesia on the opposite side of the body. If the lesion involves the dominant hemisphere and the patient is conscious, aphasia can be demonstrated. The neurological signs are those of an acute flaccid hemiplegia with diminished tendon reflexes, absent abdominal reflexes and a Babinski sign.

The mechanism by which the cerebral disorder develops appears in most cases to be an occlusion of the common carotid artery by the dissection. The effects of carotid artery obstruction have been studied by many observers (King and Langworthy, 1941; Aggeler, 1941; Fracassi, 1942). In young individuals with a normally formed circle of Willis, thrombosis or ligature of the common carotid artery is well tolerated and the cerebral blood supply is maintained. In elderly people who have rigid vessels much narrowed by atherosclerosis or in those who have an anomaly of the circle of Willis, such as an undersized anterior or posterior communicating artery a sudden occlusion of the carotid may result in infarction of all parts of the brain supplied by the three important branches of this vessel, i.e. ophthalmic, anterior and middle cerebral arteries. As a consequence the optic nerve, the lateral portions of the frontal, parietal and occipital lobes, the superior and lateral parts of the temporal lobes, the caudate and lenticular nuclei and internal capsule will undergo ischæmic necrosis. The clinical picture which then develops, sometimes referred to as "carotid hemiplegia," consists of homolateral blindness and pallor of the retina on fundoscopy, contralateral hemiplegia and hemianæsthesia as described above. Coma occurs frequently and often prevents detection of the aphasia and blindness. A pulseless common carotid artery may provide the clue for diagnosis.

In cases of dissecting aortic aneurysm other physiological factors may contribute to the cerebral anæmia. Not every case with syncope or a convulsion should be considered to have an occlusion of the carotid artery. As the blood-pressure falls to shock levels symptoms of cerebral anæmia may develop.

In the differential diagnosis of dissecting aortic aneurysm with cerebral infarction several medical diseases must be considered. Coronary thrombosis with myocardial infarction, mural thrombosis and cerebral embolism is a common sequence of events and may be difficult to differentiate.

Electrocardiographic changes and the widened aorta in the chest X-ray should distinguish the two in most cases. Acute or subacute bacterial endocarditis with myocardial insufficiency and cerebral embolism or chronic rheumatic endocarditis with auricular fibrillation and embolism may resemble dissecting aneurysm in some respects. Diagnosis will depend on finding the characteristic features of each disease. Pain in the right arm with coldness, absence of pulsations, numbness and weakness combined with a left hemiplegia which may occasionally occur when the dissecting aneurysm occludes the innominate artery may be confused with the cervical rib syndrome in which thrombosis of the subclavian artery and retrograde embolism into the common carotid artery occur (Hoobler, 1942).

SUMMARY.

Some of the most interesting complications of dissecting aortic aneurysm are those due to involvement of the nervous system. The clinical syndromes which are produced can be classified into three groups, depending on the portion of the nervous system involved.

I.—Ischæmic Necrosis of the Peripheral Nerves.

The clinical picture in these cases is that of a pulseless, cold extremity with weakness, anæsthesia and loss of tendon reflexes. The aortic dissection extends into a major artery of an extremity, interfering with its blood supply. Although the iliac and axillary arteries are the main vessels usually affected, the degree of collateral circulation probably determines whether ischæmic necrosis of the extremity will occur.

II.—Ischæmic Necrosis of the Spinal Cord.

Flaccid paralysis, urinary retention and anæsthesia below a level on the trunk characterize the clinical picture. The lesion is produced by occlusion of the intercostal and lumbar arteries by the dissection in the wall of the aorta with consequent infarction of the spinal cord. One case is reported with clinical and pathological examination of the nervous system. The spinal cord from the 5th thoracic to the 5th sacral segment was infarcted, particularly in the area of distribution of the anterior spinal artery.

III.—Ischæmic Necrosis of the Brain.

This syndrome consists of confusion, stupor or coma with flaccid hemiplegia, hemianæsthesia and aphasia (dominant hemisphere). The dissection extends into the carotid or innominate arteries and obstructs blood flow to the area of brain supplied by the anterior and middle cerebral

arteries. There is often an associated involvement of the ophthalmic artery with resultant blindness. This clinical picture is sometimes referred to as "carotid hemiplegia" and occurs only if the collateral circulation through the circle of Willis is inadequate. The histological changes are those found in any ischæmic cerebral lesion of the same age.

The importance of the neurological aspects of dissecting aortic aneurysm is indicated by the fact that the correct ante-mortem diagnosis was twice as frequent when neurological disturbances were found.

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A DISTINCTIVE TYPE OF ENCEPHALOMYELITIS OCCURRING AMONG TROOPS IN THE NORTHERN TERRITORY OF AUSTRALIA: A DISCUSSION OF TWO FATAL CASES.

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To-day pathologists recognize many different types of encephalomyelitis. Viruses, bacteria (e.g. meningococci and organisms of the *Listeria* group), and other pathogenic organisms evoke more or less distinctive syndromes according to the parts of the nervous system chiefly affected, the tempo of the morbid process, and its favourable or unfavourable termination. Some of the more acute demyelinating diseases evolve under the symptomatology of encephalomyelitis, even though the lesions are not primarily inflammatory or due to a known infective agent. A group of cases designated as encephalitis by the clinician show at autopsy no definite lesions within the nervous system; presumably they are toxic in origin.

In a wide experience of various forms of encephalomyelitis and of so-called encephalomyelitis, we have seen none with the particular histological features displayed by that described in this paper.

Report of Cases

Case 1.—Private S. was admitted to an Australian General Hospital (A) on December 12, 1942. He complained of headache, malaise, pains in the shoulder, wrist and elbow joints, and a feeling of stiffness in the fingers; all these symptoms had been present for twenty-four hours. There was no past history of rheumatism. The temperature was 101·4° F., the pulse rate 112, and the respiratory rate 22 per minute. Examination of the heart, lungs and abdomen disclosed no abnormalities. The inguinal, axillary, cervical and right epitrochlear lymph glands were enlarged. No rash was present. The case was regarded as one of the acute polyarthritis recently described by Halliday and Horan (1943); typical cases of that condition were being

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February 17 he was unable to swallow fluids. There was now paresis of the left side of the face and of the left half of the palate and pharynx, with paralysis of the left vocal cord. The excursions of the left side of the chest were diminished and the respiratory rate 28 per minute. Throughout the day frequent attempts to cough up accumulated mucus caused much distress. Dysarthria developed. During the afternoon the extremities became cyanosed. In the evening the man had a respiratory crisis, when the rate of respiration was 60 per minute. This was relieved by continuous inhalation of oxygen but was followed one hour later by acute cardiac failure and death. The patient remained conscious until a few minutes before death. At no time did he lose control of the sphincters.

Pathological examination.—Autopsy was carried out two hours after death. The body was that of a spare, young male adult. There was wasting of the muscles of the left hand, and, to a lesser extent, of those of the forearm. The leptomeninges showed considerable engorgement. The middle ears and the mastoids were clear. There was fluid blood in the cranial venous sinuses. No significant abnormality was detected in the general viscera.

When cut after fixation, affected areas of the spinal cord were found to be soft and hæmorrhagic: hæmorrhages followed the path of lesions in the brain-stem and cerebellum. The brain and cord were sectioned and stained by current neuropathological methods; the following is a description of the lesions encountered.

Ulnar nerve.—The nerve was the seat of marked residual inflammation. Many lymphocytes and plasma-cells and some eosinophils lay between the nerve fibres, many of which had undergone degeneration. The sheath of the nerve showed areas of infiltration with similar cells.

Spinal cord.—Apart from mild mononuclear infiltration of the meninges, due, no doubt, to cells trickling from above, levels of the spinal cord below the first two thoracic segments exhibited no abnormality.

In the upper thoracic and lower cervical segments meningeal infiltration was intense over the left posterior aspect of the cord and in the anterior fissure. The cells present were mainly lymphocytes, with a variable proportion of polymorphonuclear leucocytes in the vicinity of areas of severe damage to the underlying tissues, and occasional plasma-cells elsewhere. Over almost the whole cross-section of the cord at these levels the perivascular sheaths contained many similar cells, mixed or unmixed with proliferated adventitial elements. Often the cuffs were many cells deep, and on occasion inflammatory cells overflowed into the surrounding nervous tissues.

The most striking lesions in the nervous parenchyma consisted in large, sharply demarcated, focal necroses commonly attaining a diameter of 300 μ and sometimes one of 750 μ (fig. 1). They were often elongated in the long axis of the cord. Some appeared to be perivenous, in that they were disposed around one or more small veins; many, however, were not obviously related to a vessel. Their precise microscopical appearances varied. Most of the foci showed complete, or almost complete, destruction of pre-existing structures, which were replaced by a densely packed mass of living and dead leucocytes (as in a miliary abscess), by mixed polymorphonuclears and pleomorphic microglial cells, or by microglial cells together with a few lymphocytes and plasma-cells. In a few areas less clearly circumscribed the myelin sheaths were greatly ballooned, the axis-cylinders undergoing fragmentation, and the nuclei of the intrinsic cells of the tissue fading or absent; early infiltration with polymorphonuclears was evident, with signs of karyorrhexis in the nuclei of some. These less advanced areas of damage were sometimes related to small veins which had undergone thrombosis; from the findings in the brain-stem, however,

admitted to hospital at the time under consideration. The temperature subsided within twenty-four hours. During the following week the arthritic symptoms improved and on December 26 the man was considered fit for discharge.

On December 27 he complained of pain and swelling on the inner side of the left wrist. There was then some periarticular swelling on the medial side of the wrist-joint. Pressure over the ulnar nerve caused a shooting pain along the inner border of the hand and little finger. On the pulp of the left little finger was a previously unnoticed superficial laceration; it was linear and about 2 cm. long, crusted and mildly infected, and the left epitrochlear gland was enlarged and tender. The patient stated that he had cut his finger while opening a tin just before admission to hospital. With local treatment the wound healed. On January 15, 1943, tenderness still persisted along the course of the ulnar nerve below the elbow, and sensation to light touch was somewhat diminished over the left little finger and ulnar border of the hand. On the next day this sensory impairment had disappeared. On January 17 there was some aching in the left hand. This ceased, and by January 20 only tenderness along the course of the nerve persisted. On January 26 the man was transferred to a convalescent depot. Whilst there, on February 1, he complained of pain about the middle of the arm.

He was readmitted to hospital on February 11 stating that two days earlier he had had a shiver with vomiting and frontal headache. The pain in his arm had become worse, and numbness and tingling affected the medial half of the forearm and hand and the ulnar four fingers. Examination showed wasting of the small muscles of the left hand, particularly of those of the hypothenar eminence, and slight wasting of the medial group of flexor muscles of the left forearm. All movements of the left forearm, hand and fingers were weak. No fibrillation of the muscles was observed. Sensibility to temperature, pain and light touch was diminished over the fourth and fifth fingers. The muscle bellies on the medial side of the left forearm were tender. Pressure over the ulnar nerve at the elbow and in the lower part of the arm caused pain. Tendon reflexes of the biceps and triceps muscles were rather more active on the left than on the right side. There was no clinical evidence of more widespread involvement of the central nervous system. Temperature, and pulse and respiration rates were normal. On February 12, although the patient had vomited once during the night, there was no alteration in the signs apart from a rise in temperature to 100° F. (The temperature remained between 100° F. and 101° F. until the last day of his illness, when there was a slight remission followed by a rise to 102° F. a few hours before death.) The next day the neck was slightly stiff. Occasional attacks of vomiting recurred during the remainder of the illness. On February 14 the man complained of numbness and tingling in the left leg and foot. There was slight weakness in the muscles of the left leg and foot but no loss of sensation. Deep reflexes were active and equal.

On February 15 the neck-stiffness was more definite. Lumbar puncture yielded an opalescent fluid under increased pressure. After centrifuging, the supernatant fluid was clear. Total protein was 70 to 80 mgm. per 100 c.c. of fluid. The count was 633 cells per c.mm., with lymphocytes and mononuclear cells predominating. No organisms were detected in smears stained by the Ziehl-Neelsen or Gram's method; no growth occurred on blood-agar. In blood-films malarial parasites were not detected. Cultures from the nose and throat yielded no growth of *C. diphtheriæ* on Loeffler's medium; on blood-agar *Staph. albus* was the predominating organism.

On the following day the patient complained of numbness over the left side of the chest and showed some general asthenia of the facial musculature. In the evening he swallowed with difficulty and experienced considerable discomfort while nasal washings were being collected for animal inoculation. On the morning of

of one side and in the restiform body of the opposite side; in the *formatio reticularis* generally on the side of the affected fillet and in the cerebellar connections of this side they were much less severe. At higher levels the area involved diminished sharply, and at the upper limits of the pons lesions were limited exclusively to the region of the medial fillet; here, too, necrosis of the vessel walls and thrombosis were minimal, as might be expected at an early stage if these processes were concomitant or secondary. At still higher levels no lesions were detected. In the cerebellum the dentate nucleus and white matter on one side suffered severely; lesions extended far into the white matter of the folia, and in places "jumped" the granular layer to involve stretches of Purkinje cells and adjacent areas of the molecular zone. Minor cellular infiltration appeared in some of the cranial nerves, suggesting outward spread from the brain-stem.

Cerebrum.—The only abnormality detected was the presence of a few inflammatory cells and macrophages in the meshes of the pia-arachnoid.

Experimental investigation.—Defibrinated blood, cerebrospinal fluid and nasal washings collected on the day before death were frozen and sent by air to Adelaide; they arrived in less than two days at a final temperature of −4° C. The nasal washings were filtered through a Berkefeld N filter. Inoculated intratesticularly and intracerebrally into rabbits, intracerebrally and intramuscularly into guinea-pigs, and intracerebrally into mice these fluids evoked no signs of disease. Inoculation into developing hens' eggs (Miss Jessica Mawson) also proved fruitless.

A piece of cerebral cortex collected at autopsy was placed in 50 per cent. buffered glycerin and despatched similarly. Unfortunately, as mentioned above, subsequent examination showed that the higher regions of the nervous system were free from appreciable change; probably, therefore, they did not harbour the infective agent. However this may be, inoculations into rabbits, guinea-pigs, mice, developing eggs and a monkey (*Macaca irus*) led to no results. No pathogenic organisms were cultured from the brain.

Case 2.—Private R. was accidentally shot in the left thigh on December 20, 1942. He was admitted to an Australian General Hospital (B) where the edges of the through-and-through wound were excised and he was given sulphanilamide. There was no bone injury. On December 21 he was transferred to another Australian General Hospital (A) where on January 20 four teeth were extracted. Two days later though afebrile he complained of headache, which was relieved by aspirin. On February 4 his tonsils were removed and on February 11 he became febrile. There was no evidence of dengue fever. Next day the man felt very well and his temperature was normal. Repeated examinations for malarial parasites were negative. On February 19 he returned to his unit. During the journey by hospital train he felt sick and vomited. After reaching his unit, a small detachment without a medical officer, he felt very ill, developed headache and vomited persistently. For the next five days he lay in his tent in this condition. On February 25 he experienced diplopia and next day was readmitted to an Australian General Hospital (B) complaining of severe headache, nausea, vomiting and double vision.

He was then very ill, dehydrated and cyanosed, but alert mentally. The tongue was dry and furred. The tonsillar regions were covered with a whitish-yellow membrane, as though several days after tonsillectomy. The neck was rigid and Kernig's sign present. Rapid nystagmus was present on looking to the right and to the left. Diphtheria bacilli were not present in smears or culture. The white blood cells numbered 20,000, of which 80 per cent. were neutrophils. The cerebrospinal fluid was clear; it contained 250 lymphocytes per c.mm. and 50 mg. protein per cent.

In spite of continuous infusions of glucose-saline and intravenous sulphapyridine

it was clear that many of the lesions originated independently of thrombosis, which when present was a concomitant rather than the cause of the necrosis.

For a variable distance around the necrotic foci the nervous tissues were diffusely infiltrated with leucocytes, or showed proliferation of the microglia and early reaction of the neuroglia. In such regions the vessels often showed considerable multiplication of adventitial cells, and the smaller ones marked swelling of their endothelium. Around a few veins at some distance from the most severe lesions, a collar of granular corpuscles or of polymorphic microglial cells marked a narrow concentric zone of extra-adventitial destruction of the myelin sheaths and axis-cylinders. Many small and recent hæmorrhages were present in the parts most affected. None of the lesions contained neutral fat.

In the 8th cervical and 1st thoracic segments, the intramedullary lesions involved chiefly the tip of the left posterior horn, the entry-zone of the left posterior nerve-roots, and the nerve-roots themselves. At higher levels the left posterior column suffered most damage, and lesions in the left posterior horn and ventral to the right anterior horn were less severe or less extensive, or both. The pathological process did not select for destruction and neuronophagia nerve cells outside the limits of a necrotic focus; thus the anterior horn cells were wholly normal except at levels corresponding to the origin of the ulnar nerve, where those on the left side exhibited axonal reaction (chromatolysis). In the meninges at one level the wall of a vein in the anterior fissure was necrotic (see later). As stated, perivascular cuffing was widespread.

Brain-stem and cerebellum.—In general the changes resembled those in the cord, except that they were at a rather earlier stage and the events leading up to venular occlusion were easier to follow. Meningeal infiltration was slight.

Many large foci of necrosis with massed polymorphs or other cells occurred in the absence of thrombosed veins (fig. 2). In or near some of these foci, and also independently, the walls of some veins had undergone necrosis together with a narrow concentric zone of the surrounding nervous tissue. The perivascular spaces were distended with fibrinous exudate. The extra-adventitial tissues stained a brighter orange than usual with van Gieson's stain and a deeper red with eosin; cells normally present had disappeared and many polymorphs and microglial cells had accumulated in their place. The vessel wall, similarly infiltrated, was affected from without inwards; in many cases the endothelium was still intact and the lumen patent (fig. 3). In those veins which showed thrombosis the endothelium had ceased to exist, at any rate as a continuous layer. Over some otherwise unaffected areas related to the largest veins occluded, the nervous tissues showed changes suggestive of impending ischæmic necrosis (fig. 4). It was clear, therefore, that while venous thrombosis occurred in the vicinity of some necrotic foci, this was not invariably the case; it resulted from participation of the vessel wall in the pathological process responsible for the formation of necrotic foci, and was not the cause of the latter. The appearances suggested, however, that survival of the patient for a longer period would have allowed the full development of larger areas of necrosis due to the circulatory disturbances resulting from this thrombosis.

Diffuse leucocytic infiltration and microglial overgrowth was more prominent than in the cord. Perivascular cuffing was more widespread than were other changes; in the perivascular sheaths of some vessels the cellular exudate consisted almost wholly of polymorphs widely spaced as though separated during life by œdema-fluid.

The distribution of these changes was informative. At various levels of the medulla they occurred over much of the cross-section. In the lower parts of the pons they were localized very nearly to two regions, in and around the medial fillet

at 4-hourly intervals, his condition deteriorated rapidly. He vomited dark brown, bloody material.

On the morning of February 27 he had paresis of the external rectus muscles of the left eye. The red blood corpuscles were then 7,000,000 per c.mm., the hæmoglobin 115 per cent. and the white cells 48,000 per c.mm. Intravenous fluid was continued but the man died soon after midday.

Pathological examination.—Except in the nervous system there were no significant macroscopic findings. Culture of the cerebrospinal fluid was sterile.

Lesions in the brain-stem and cerebellum were identical in character with those in the preceding case. The foci of necrosis were, however, more numerous and larger, attaining sometimes a long diameter of 1·6 mm. In places they were almost confluent, thus producing large areas of destruction several millimetres across. Diffuse infiltration of the tissues again was marked, as were the vascular changes described above. There was no particular involvement of nerve cells at a distance from the foci, and meningeal infiltration was insignificant.

These lesions were most severe in the dorsal and lateral parts of the pons, in the *brachium pontis*, and in the white matter of the cerebellum as far as the nearer folia. In the mid-brain they were much less extensive and were confined to the dorsal half of the organ ventral to the *iter of Sylvius*. At levels above the mid-brain no lesions were detected.

The trigeminal nerve-roots showed marked inflammation.

Résumé

In early December, 1942, the first patient suffered from the recently described acute polyarthritis (Halliday and Horan, 1943). Just before admission to hospital for this condition he had cut his left fifth finger; the small, mildly infected laceration healed in the course of three weeks or so. Coincident tenderness along the course of the ulnar nerve persisted throughout his stay in hospital and at a convalescent depot. Early in February, 1943, he complained of pain in the middle of the arm; eight days later he had a rigor, vomited and developed headache. Signs of motor and sensory disturbance were now pronounced in the left arm. In the last five days of life, fever, occasional vomiting and neck-rigidity were followed by paræsthesiæ and slight weakness in the left leg and foot, numbness of the left side of the chest, loss of function of the lower cranial nerves and respiratory embarrassment. Death occurred from acute cardiac failure about ten weeks from the date of injury. Two days before death the cerebrospinal fluid showed a well-marked pleocytosis (633 cells, mostly mononuclear, per c.mm.).

Cerebral symptoms in the second case followed fourteen days after tonsillectomy. The wounds were then still unhealed. In this case the period intervening after trauma was shorter, possibly because the infective agent entered at a point nearer the neural axis.

The total histological picture in the two cases was identical and distinctive. Its components included:—

(i) Sharply demarcated focal necroses of the nervous tissues with the accumulation of densely packed polymorphs or microglial cells, or both.

(ii) Necrosis of the walls of small and medium-sized veins, which were infiltrated with inflammatory cells and fibrin and surrounded by a narrow zone of extra-adventitial necrosis. Necrosis of the whole thickness of the wall resulted in thrombosis, which threatened with destruction still wider areas of nervous tissue.

(iii) Diffuse cellular infiltration of adjacent tracts of nervous tissue, perivascular cuffing and other reactive changes in near and more distant vessels, and petechial hæmorrhages.

For the most part these changes occurred in areas of the white matter or in those where white and grey matter were intimately mingled; they did not extend to parts of the neural axis above the brain-stem. There was little or no tendency to involvement of nerve cells outside the areas of necrosis. In most regions meningeal infiltration was negligible and obviously secondary to the parenchymatous lesions.

The bacteriological findings in these cases were essentially negative. No pathogenic micro-organisms were isolated from the body-fluids or brain of Case 1 or from the cerebrospinal fluid of Case 2. In appropriately stained sections, no bacteria, protozoa, yeasts or rickettsiæ could be detected. In Case 1 intranuclear bodies in very occasional endothelial cells might possibly have been small acidophilic inclusions, but this was far from certain in the formalin-fixed material alone available for study. No such structures occurred in Case 2. Limited experimental studies yielded negative results. The probable ætiological factor, therefore, is a matter for conjecture.

Discussion

The clinical history and the distribution of lesions in Case 1 point unequivocally to the spread of a pathogenic agent from the lacerated wound on the left little finger by the nervous pathway to the spinal cord; from the segments of entry into the cord the distribution of lesions along sensory tracts is hardly less clear. In Case 2 the history of previous tonsillectomy suggests the site of entry of the pathogenic agent; it is now well recognized that the virus of poliomyelitis commonly enters the body following this operation. The absence from both brains of a generalized meningitis, the bacteriological sterility of the cerebrospinal fluid, and the failure microscopically to detect bacteria in the nervous lesions speak on

the whole against a bacterial ætiology. It is true that *Listeria* infections in some species of animals (Gill, 1931, 1933; Jones and Little, 1934; and personal observations) lead often to an encephalitis rather than to a meningitis. Multiple foci of softening develop chiefly in the brain-stem and upper cord; in many ways they resemble those in the cases under discussion. We have not, however, observed necrosis of the vessel walls as part of the pathological picture in *Listeria* infections. In this type of encephalitis the causative organisms can usually be demonstrated in sections of the brain, and they grow easily in cultures; they penetrate the central nervous system from the bloodstream, at any rate in some animal species (Burn, 1935). On the other hand, as we have shown, in the cases described in the present paper the mode of spread of the pathogenic agent tallies very closely with that of a number of filtrable viruses. While almost absolute integrity of nerve cells not actually involved in an area of focal necrosis is not characteristic of infections with neurotropic viruses, in at least one virus infection (canine distemper) the white matter tends to be selectively involved, and the nerve cells are relatively less affected than in most virus diseases of the central nervous system (*see* Hurst, Cooke and Melvin, 1943). We hope that further opportunity of deciding the ætiology will present itself.

An observation worthy of brief comment is the necrosis of vessel walls in this and other diseases. This lesion has received little attention from neuropathologists. In the present case only the small and medium-sized veins suffered; in our experience the arterioles suffer in this manner very much less frequently than do the veins, though the former may participate when the infecting agent is a highly virulent virus and the extent of local damage is considerable. Veins so affected, on the other hand, may lie in otherwise normal tissue, except for a narrow concentric zone of extra-adventitial necrosis. The phenomenon thus appears to be distinct from that of, say, caseation of the wall of a vessel embedded in a mass of tubercular granulation tissue. The outer coats of the vessel are the first to sustain damage, and only later does the endothelium succumb with consequent thrombosis and further injury to the nervous substance. The phenomenon has been recorded in the brain and other organs infected with B virus (Sabin and Hurst, 1935), in the skin in infectious myxomatosis (Hurst, 1937), in the brain in human infection with an unidentified virus (Swan, 1943), and in the spinal cord of a case of canine distemper (Hurst, Cooke and Melvin, 1943); it will be noted that, whatever their other tropisms, the viruses mentioned all possess considerable affinity for mesodermal tissues. Similar appearances obtain in the brain in acute hæmo-

rrhagic leuco-encephalitis (Hurst, 1941). Why veins of a particular range of calibres should suffer predominantly is not clear, unless it be that their walls are less resistant owing to their very imperfect musculature. It will also be noted that in the encephalomyelitis following vaccinia and other exanthemata the zones of perivascular demyelination surround veins of similar dimensions. From observations on acute hæmorrhagic leuco-encephalitis, canine distemper and the effects of such chemical poisons as KCN and NaN_3, Hurst (1942) concluded that demyelination represents the reaction of the white matter to injuries short of those causing necrosis. It seems probable, therefore, that the localization of necrosis in and around the walls of the veins and of demyelination in the nervous tissues immediately surrounding them are linked phenomena of considerable significance in neuropathology.

Summary.

In this paper we have described a distinctive and apparently undescribed form of encephalomyelitis of unknown ætiology. Entering peripherally, the pathogenic agent apparently travels by nerve-paths to produce sharply demarcated focal necroses of the nervous tissues; it has no especial predilection for the nerve cells. The walls of the small and medium-sized veins suffer necrosis; the surrounding tissues are necrotic or are infiltrated with various inflammatory cells. When necrosis involves the vascular endothelium thrombosis occurs and threatens with destruction still wider areas of nervous tissue. Many diverse appearances can be attributed to these essential changes. The lesions are limited in their distribution.

The phenomenon of necrosis of the venular walls and adjacent tissues is discussed briefly, and a relation seen to the demyelination which in some diseases occurs around veins of similar calibre.

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LEGENDS TO PLATE.

FIG. 1 (*Case 1*).—Low-power view of the middle cervical cord showing large focal necroses situated chiefly in the posterior column of the left side, marked perivascular infiltration, &c. Hæmatoxylin and van Gieson's stain.

FIG. 2 (*Case 1*).—Pons. Focal destruction of the nervous tissue with infiltration by necrotic polymorphonuclear and microglial cells. Hæmatoxylin and van Gieson's stain.

FIG. 3 (*Case 1*).—Pons. Cellular infiltration of the tissues around a vein. The wall of the vessel is largely necrotic but the endothelium is intact and the lumen patent. Hæmatoxylin and van Gieson's stain.

FIG. 4 (*Case 1*).—Pons. A thrombosed vein with completely necrotic walls. The surrounding tissues show signs of impending necrosis *en masse*. Hæmatoxylin and van Gieson's stain.

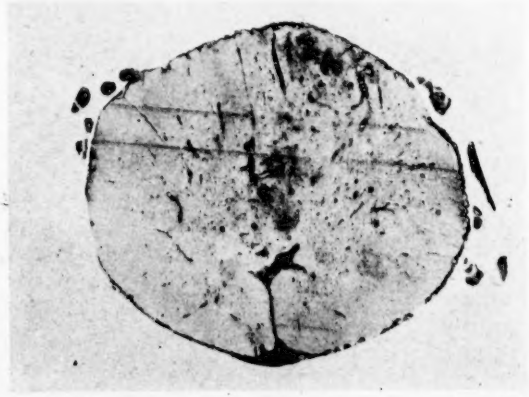

FIG. 1.

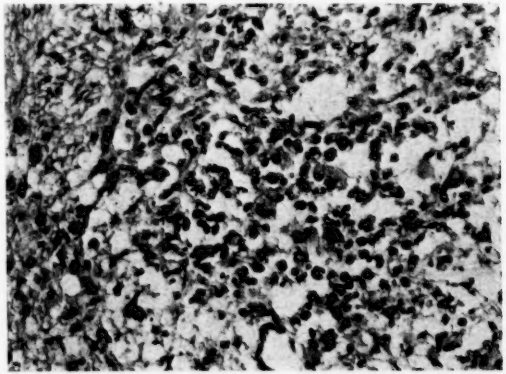

FIG. 2.

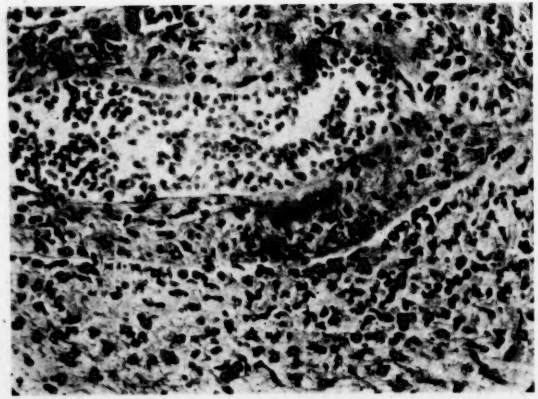

FIG. 3.

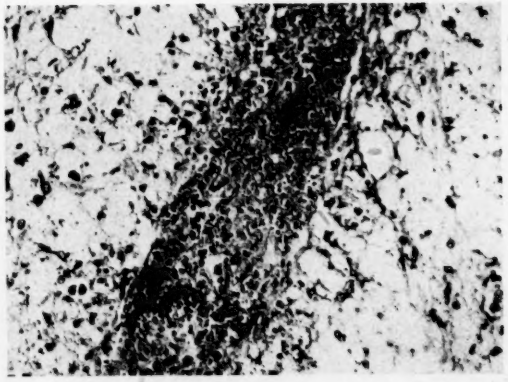

FIG. 4.

To illustrate article by Lieut.-Col. John P. Horan, Major George A. W. Johnston, Lieut.-Col. John H. Halliday, Major J. O'Brien, and E. Weston Hurst.

A REVIEW OF SOME RECENT OBSERVATIONS ON DEMYELINATION.

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THE so-called demyelinating diseases of man and animals comprise a variety of morbid processes of the white (and grey) matter from which we exclude tract degenerations, gross softenings resulting from vascular occlusion, and other lesions clearly of a secondary nature. The ætiology of the diseases occurring in man is unknown, and together they constitute one of the outstanding unsolved problems of neuropathology, interest in which increases year by year. In the absence of definite knowledge of their causation, they have mostly been described by names indicating the anatomical distribution or histological characters of the nervous lesions. Some authors (Ferraro, 1937; Hurst, de Crespigny and Fry, 1939; Hurst 1941*b*) have doubted the wisdom of indefinite subdivision on the basis of possibly unimportant differences in the site of a lesion and its finer histopathology, especially since opinions differ widely on the lines of demarcation between the entities thus postulated.

Until recently, those seeking knowledge regarding the causation of the demyelinating diseases have confined themselves to attempts to reproduce a particular disease, usually disseminated sclerosis. It cannot be claimed that these efforts have met with greater success than have the intensive clinical and histopathological studies of the malady. Of late, however, more attention has been devoted to demyelination as a process, whether occurring as a feature in many pathological states of the human nervous system or as a lesion in animals following very diverse experimental procedures. As yet this new trend of inquiry has not led to a fuller understanding of those diseases of man in which demyelination is prominent, though as we shall see in the summary we already appreciate better the significance of demyelination as a process.

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In following these developments we shall, as far as possible, consider them in the light of the various hypotheses advanced regarding the causation of the demyelinating diseases of man.

Vascular Blockage and Demyelination.

Some early writers on disseminated sclerosis believed that thrombi play an essential part in the genesis of the demyelinated plaques. Later observers regarded thrombi when present as secondary to the other changes of the disease, or failed to detect them; many, however, described a more or less close relationship of the lesions to the smaller vessels. Hassin's contention (1937), that in disseminated sclerosis there is a diffuse degeneration of the myelin wholly unrelated to the vascular supply, represents the viewpoint at the other extreme.

In recent years Putnam and his colleagues have warmly championed obstruction of the small veins as the factor determining loss of myelin in both disseminated sclerosis and disseminated encephalomyelitis; the latter Putnam (1936*a*) regards as a more acute condition closely allied to disseminated sclerosis, from which it cannot be separated sharply. In both diseases (Putnam, 1936*b*, 1937*a;* Putnam and Alexander, 1939) venular thrombi may occur in the nervous system and in other organs; with many stains they are not demonstrated easily, and they may disappear rapidly from the lesions. Closure of the vessels by fibrous plugs or by endothelial cells is even more common than is recognizable thrombosis. Scheinker (1943*a*) also regarded vascular changes, particularly occlusion by a thrombus (which is not always easy to identify), as an essential feature in the pathogenesis of the demyelinated plaques of disseminated sclerosis. Simon and Solomon (1935) and Simon (1942) found evidence of increased coagulability of the blood when patients received injections of adrenalin or of typhoid-vaccine. Dattner (1937), however, stated that the clotting-time of the blood is increased in many cases of disseminated sclerosis. Marburg (1942), while agreeing that local degeneration of myelin may result from phlebothrombosis, regarded the latter as only one of the ætiological factors of the disease. Dow and Berglund (1942), in a meticulous study of 60 plaques from 5 cases of disseminated sclerosis, observed that only two-thirds were oriented in the form of elongated collars around small veins, and that in 51 no signs of thrombosis were evident. They questioned the facile disappearance without trace of thrombi which had existed sufficiently long to cause demyelination, and suggested that when present they might be due to local absorption of thromboplastic substances released by the breakdown of myelin.

It may here be interpolated that, according to classical belief, in disseminated sclerosis and some other diseases the damage to the myelin sheaths is primary, and is accompanied by relatively less injury to the axons. On this point the writings of Putnam *et al.* are not consistent. Recently, however, Alexander and Putnam (1940) have maintained that often the appearance of preservation of the axons is an optical illusion, and that in fact both structures are damaged simultaneously, although the axons are slightly more resistant to complete destruction.

In various publications Putnam *et al.* have recorded experimental evidence which they believe supports their views summarized above. Putnam, McKenna and Morrison (1931) injected cod-liver-oil emulsions into a carotid artery of eight cats and seven dogs, with the object of obstructing long stretches of rather large vessels. Areas of demyelination were present in four animals killed from twenty days to five months later. The histological appearances could be "matched with great accuracy in almost any early case of multiple sclerosis." Later (1935) Putnam described a method of blocking the cerebral venules by means of oil injected into an isolated section of the superior longitudinal sinus. The *later* stages (up to ten months) of the lesions so produced consisted in plaques of demyelination with almost complete preservation of the axons and dense fibrous gliosis confined to the white matter. Although these plaques did not reproduce all the features of those in multiple sclerosis, the resemblance was sufficiently close to suggest venular thrombosis as an essential antecedent in the human disease. Incidentally, Putnam (1937*a*) also recorded demyelination as a sequel to thrombosis of the pial veins in human meningitis. Hoefer, Putnam and Gray (1938) found that coagulants of many types injected into the circulation may produce thrombi in the central nervous system; in their long-term experiments the resulting cerebral lesions resembled closely those of post-vaccinal and similar forms of encephalomyelitis in man. The authors pointed out that brain-extracts, such as those used by Rivers *et al.* to produce experimental demyelination (*see below*), possess considerable coagulating properties. It is only fair to add that Putnam's views regarding the resemblance of the lesions he produced experimentally to those in disseminated sclerosis, &c., have not been accepted unreservedly by all neuropathologists who attended the meetings at which he read his papers.

Injecting for other purposes an olive-oil egg-yolk "mayonnaise" into one carotid artery of sheep, pigs and monkeys, Hurst and Cooke (1943) observed that despite the small size of the globules lesions often developed in the nervous system. They occurred where (1) many closely adjacent

capillaries were blocked by globules of fat; (2) an unusually large globule had lodged; and (3) the capillaries and rather larger vessels became occluded by peculiar hyaline plugs quite distinct from ordinary thrombi. Apparently these plugs disappeared within a very few days of injection. The obstructing globules of fat also disappeared progressively, so that examination of the brains in any but the earliest stages afforded no true idea of the number of vessels initially blocked. Lesions in the white matter were more numerous and/or more severe than those in the grey. The former ranged from areas in which there was damage to only a few myelin sheaths and axis-cylinders to those in which full necrosis of tissue had occurred; demyelination (with destruction of axons), however, was much more common than was necrosis. In the later stages, necrotic areas were replaced by massed granular corpuscles seldom intermingled with collagen fibrils, while in less affected areas the microglia was largely polymorphic and glial sclerosis marked. The distribution of the lesions was similar to that of the areas of demyelination or necrosis in some animals poisoned with potassium cyanide (*see below*).

These findings recalled those of various observers in cases of fat-embolism in man. Greenfield (1941) described in the white matter areas of destruction of myelin and axis-cylinders but seldom true necrosis; the areas were "quite unlike those seen in any other condition." Winkleman (1942) also observed demyelination in cerebral fat-embolism. Scheinker (1943*b*) found that the most constant and uniform pathological changes in the brain were circumscribed areas of demyelination and necrosis lying mostly in the white matter. He considered them similar to the early lesions of disseminated sclerosis.

We cannot doubt, therefore, that demyelination with degeneration of axis-cylinders may be a sequel to relatively minor obstruction of the circulation in the white matter, an obstruction insufficiently important to lead to complete necrosis. The peculiarities of the cerebral circulation in relation to demyelination and other types of nervous lesion have been considered by Putnam (1937*b*). Certain obstructing plugs produced under experimental conditions apparently disappear rapidly from vessels in the lesions to which they have obviously contributed, but there is no present evidence that this observation has any bearing on human pathology. It is doubtful whether the experimental lesions considered above really tally with those in the demyelinating diseases of man.[1]

[1] Some of these lesions, however, together with some of those produced by chemical anoxia (*see* next section), bear distinct resemblances to those in Binswanger's disease and in the condition described by Marchiafava and Bignami.

THE EFFECTS ON THE BRAIN OF ANOXIA DUE TO CHEMICAL SUBSTANCES.

The anoxia which obtains during poisoning with a number of chemical substances may lead at times to profound changes in the cerebral white matter.

Ferraro (1933*a* and *b*) administered potassium cyanide to cats and monkeys. After repeated doses he obtained lesions distributed similarly to those of diffuse sclerosis. Usually they were not sharply defined, but occasionally foci like those in disseminated sclerosis or, alternatively, concentric demyelination as described in man by Balò were present. The U-fibres were usually intact. Changes were particularly severe in the frontal and occipital lobes, and especially in the periventricular regions and the corpus callosum. The optic nerves and tracts, brain-stem, cerebellum and spinal cord also suffered. In demyelinated areas the axis-cylinders were often relatively spared, and considerable gliosis had occurred; the loss of myelin could not be correlated with involvement of the oligodendroglia. A few areas of complete necrosis had resulted where degenerative changes were particularly severe. Only 2 of 18 animals showed inflammatory lesions in the white matter, cortex and meninges. No emboli or thrombi were detected.

In general these results were confirmed by Jervis (1937), Jedlowski (1937, 1938) and Hurst (1940, 1941*b*, 1942). The last, however, in monkeys produced demyelination only in the cerebral hemispheres and optic tracts, and noted no predilection of the lesions for the periventricular regions.

Hurst analysed the conditions under which cyanide causes demyelination and showed that the effects of the poison vary considerably with dosage. Massive single or repeated doses usually damaged chiefly the cerebral or cerebellar cortex. Repeated (less often single), rather smaller doses led to bilateral necrosis in the basal ganglia, especially the globus pallidus, or in the cerebral white matter, or in both. In a remarkable manner, necrosis often developed suddenly and simultaneously over wide tracts of the white matter after a dose of the poison tolerated previously on many occasions; the areas affected included the centrum semi-ovale, corpus callosum, anterior commissure, and so on. Less extensive lesions occupied a central position in the tongues of white matter projecting into gyri of the occipital, temporal and parietal lobes. In small lesions of the grey matter the allegedly more vulnerable nerve-cells might escape severe damage when myelin sheaths and axons were destroyed. Accompanying leucocytic infiltration was often much more marked than might have been expected in a condition of purely toxic origin. With repeated, still smaller doses over a longer period, the grey matter usually escaped damage and

lesions were confined to the white matter. Demyelination, with loss of axis-cylinders, became almost complete in the regions mentioned above. The optic tracts suffered to a lesser degree and the optic nerves still less. The U-fibres were partially spared, while the internal capsules and optic radiations showed considerably greater resistance. These lesions were not progressive once the doses of cyanide were discontinued; their presence did not determine the occurrence of post-vaccinal encephalitis in animals infected with vaccinia while receiving daily doses of cyanide.

The anoxia occurring in poisoning with potassium cyanide is "histotoxic," that is, it results from inhibition of the intracellular oxidative ferments. Another chemical substance with a similar, though less evanescent, action in sodium azide. With this also Hurst produced in the white matter of monkeys necrosis or demyelination according to the amounts administered. The optic nerves and tracts were affected almost constantly; only occasionally were marked changes present in the centrum semi-ovale. Necrosis in the optic connections followed single or repeated large doses leading to lengthy unconsciousness, or developed abruptly from summation of the effects of many small doses each insufficient to evoke marked nervous symptoms; the blindness occurring abruptly under the latter circumstances presented superficial analogy to the sudden visual disturbance heralding the onset or marking a recrudescence of disseminated sclerosis in man. These sudden marked effects could not be explained on the basis of mere accumulation of the poison in the system; it seemed probable that repeated small insults brought the nervous tissues to a state in which a further small dose of the poison, one normally tolerated, produced the most serious consequences. This observation recalled the equally abrupt necrosis occurring with constant daily doses of cyanide, which certainly is not a cumulative poison. With prolonged poisoning by small doses of azide, partial demyelination occurred in the optic nerves or tracts. Necrosis in the striatum was more frequent and more severe than in poisoning with cyanide; the cerebral and cerebellar cortex, globus pallidus, &c., suffered less constantly and less severely.

Wyndham (1941; *also see* Hurst, 1942) was unable to demonstrate a biochemical basis for the demyelination caused by these chemical agents. Though *reversible* inhibition of the oxidative ferments undoubtedly accounted for the immediate symptoms of poisoning with cyanide, *irreversible* inhibition was not brought about *in vitro* with concentrations of the chemical far greater than those likely to obtain *in vivo*. No decrease in oxidative ferments occurred in the white matter of monkeys long poisoned with cyanide. Wyndham failed also to find any alteration in

the polydiaminophosphatide, cerebroside, polydiaminophosphatase and cerebrosidase of animals poisoned with cyanide and azide.

Other observations suggest that the demyelination produced in the manner outlined above is not a specific effect of poisoning of the intracellular ferments. Carbon monoxide possesses an affinity for hæmoglobin many times that for the respiratory ferment of cells; thus Haggard (1922) found that nerve-cells of the chick may live and grow normally in the presence of as much as 80 per cent. CO (and 20 per cent. O_2). Yet clinical and experimental evidence is forthcoming that the anoxia of poisoning with carbon monoxide may be followed by demyelination. In man, Stewart (1920), Grinker (1925), Strecker, Taft and Willey (1927), Meyer (1928*a*), Hsü and Ch'eng (1938), Jacob (1940) and Eros (1942) have described more or less extensive demyelination of the cerebral white matter, with or without the familiar bilateral necrosis of the globus pallidus long considered pathognomonic of poisoning with the gas. Experimentally Meyer (1928*b*), Putnam, McKenna and Morrison (1931) and Yant *et al.* (1934) have produced demyelination or necrosis in the white matter of animals exposed to the gas. As in the case of the spontaneous demyelinating diseases of man, many observers have attributed these lesions to vascular factors such as dilatation and stasis or thrombosis, factors which do not appear to operate in poisoning with cyanide and azide.

Similarly O'Brien and Steegmann (1938) have recorded necrosis in the parietal and occipital white matter after anæsthesia with nitrous oxide; their illustration is strongly reminiscent of the more acute lesions produced by cyanide.

Hurst (1942) noted early changes in the white matter of monkeys given repeated doses of barbiturates.

In short, the anoxia occurring during intoxications with a variety of chemical substances may be followed according to its severity and duration by a number of cerebral lesions. These form a continuous series with cortical necrosis at the one extreme and demyelination of the white (or grey) matter at the other. The white matter and the basal ganglia tend to suffer under rather similar circumstances. (For a list of poisons, &c., known to condition necrosis of the basal nuclei, *see* Hurst, 1942.) The cortex possesses a much greater reducing power and has much more need of oxygen than does the white; a very severe degree of anoxia of relatively short duration may be expected to produce major damage here. The white matter is deficient in oxidase ferments and its capillary anastomoses are comparatively poor; its recuperative power, therefore, may be less than those of the cortex. It seems possible that single periods of less intense

anoxia, or a repetition of relatively minor insults each insufficient permanently to damage the grey matter, may be responsible accordingly to their intensity for necrosis or demyelination of the white matter.

Antibodies to Brain-Tissue and Demyelination.

The fact that one of the predisposing causes of the post-vaccinal type of encephalomyelitis is antirabic vaccination has suggested to some workers that the nervous lesions are somehow associated with the development of specific antibodies for nervous tissue.

Among others, Heimann and Steinfeld (1928), Witebsky and Steinfeld (1928), Plaut and Kassowitz (1929) and Lewis (1933) have produced brain-specific antisera by injecting rabbits with suspensions of heterologous brain-tissue, or with alcoholic extracts of homologous or heterologous brain "activated" by a foreign protein. The various sera so prepared react strongly in the complement-fixation test alike with suspensions and with alcoholic extracts of the brains of all species tested, both warm-blooded and cold-blooded. (They react also with cholesterol (Lewis, 1933) and with suspensions and extracts of testicular tissue.) Suspensions of normal homologous brain are not antigenic, but Schwentker and Rivers (1934) showed that autolysis or disease (vaccinial infection) may so alter the nervous tissues as to render them antigenic when inoculated into animals of the same species. The specific brain-antigen is six times as abundant in white matter as in grey, and it appears to parallel the development of myelin in the maturing animal (*see also* Bailey and Gardner, 1940, 1942). Plaut (1933) found it absent only from the anterior lobe of the pituitary. In the opinion of Schwentker and Rivers, the demonstration of a brain-specific antigen "strengthens materially the hypothesis that the encephalomyelitis which follows antirabies vaccination, if not the entire group of postinfection encephalitides, is in some manner associated with the development of specific antibodies for brain." On the other hand, Weichsel and Salfeld (1936), by means of complement-fixation tests, could not demonstrate antibodies to brain in human beings immunized against neurotropic virus diseases with material containing nervous tissues. From (unpublished) experiments carried out in sheep and rabbits by Miss Nancy Atkinson and myself, it seems highly improbable that the amount of brain administered to such patients is sufficient to produce demonstrable antibodies in the serum.

Seeking experimental evidence to support their contention, Rivers *et al.* (1933, 1935) injected monkeys intramuscularly over a period of months

alternately with aqueous emulsions and alcohol-ether extracts of sterile normal rabbit-brain. In their second series of experiments seven of eight rhesus monkeys developed nervous lesions, while controls maintained under similar conditions did not. Cultures of affected tissues were bacteriologically sterile and contained no infective agent transmissible to monkeys, rabbits, guinea-pigs or mice. The pathological changes, characterized by demyelination, occurred in relation to the blood-vessels, though in advanced lesions this relationship was obscured. They were more severe in the white matter, and especially in the pons, cerebellum and around the ventricles. The spinal cord was seldom affected. Thrombi were not observed. The authors described in some detail the cellular changes, in which eosinophilic infiltration played an important part. Multinucleated giant-cells and "globoid" cells developed at an early stage and were followed by numerous granular corpuscles. Fragments of broken myelin sheaths often appeared like large bacteria or as globules within phagocytic cells.

Innes and Shearer (1940) administered suspensions of rabbit-brain to sheep and lambs thrice weekly for a year without reproducing these results. Using suspensions of human brain combined with alcohol-ether extracts of rabbit-brain in monkeys, and suspensions of pig-brain in sheep and rabbits, I (unpublished experiments) was equally unable to produce demyelinating lesions within the space of a year.

Ferraro and Jervis (1940) were more successful. They treated seven monkeys as above for from four to thirteen months. Progressive neurological signs developed in all but one; these began after a minimum period of 100 days. The chief pathological changes consisted in perivascular areas of cellular infiltration and demyelination, with much destruction of axis-cylinders; gliosis was evident usually in the surrounding normal tissues rather than in the affected areas. The infiltrating cells consisted of granular corpuscles or, less often, of lymphocytes, plasma-cells and polymorphonuclears and eosinophils. Many peculiar multinucleated giant-cells were present in areas most severely involved. Larger demyelinated areas resulted from confluence of individual lesions. In addition, in two animals areas of partial demyelination existed showing no obvious relationship to the vessels. The lesions lay mainly in the centrum semi-ovale and white matter of the cerebellum and pons, but on occasion the cerebral cortex, basal ganglia, optic tracts, and so on, also suffered. The authors found no evidence of vascular occlusion by thrombi or emboli. Balser (1940) presented partial confirmation of these results.

We may mention here that Jervis *et al.* (*see below*) also attributed some

of the lesions found in their monkeys repeatedly injected intracerebrally with foreign proteins to the action of antibodies against nervous tissue.

Hurst and Atkinson (unpublished experiments) injected into pigs the sera of sheep or rabbits immunized over periods of many months with large doses of pig-brain. In the complement-fixation test these sera reacted with pig-brain. (Antigen in dilutions up to 1:64 completely fixed 2 M.H.D. complement; the antiserum was diluted 1:2·5 or 1:5) The pigs received intrathecally from 1 to 3 doses of 5 or 10 c.c. of serum in from one to six days; they were killed three days after the last dose. Lesions consisted in widespread meningitis and choroiditis, largely polymorphonuclear, with cuffing of many vessels in the nervous parenchyma. Control sera evoked a less intense, mononuclear reaction. No demyelinating lesions developed even when large doses of hypertonic saline were given intravenously to promote maximum contact of the serum with the nervous tissues. Hurst obtained essentially similar results in monkeys inoculated with the serum of rabbits or goats immunized with monkey-brain.

Allergy and Demyelination.

That an allergic or anaphylactic reaction may constitute the basis for certain forms of demyelination has appeared likely to some observers since encephalomyelitis complicating vaccinia and the exanthemata became relatively common.

Glanzman (1927) first made the suggestion, which was considered also by Paul (1928), Priesel (1929), van Bogaert (1932), and others, and especially by Finley (1938). In this connection Finley defined allergy as "the specific biochemical reaction produced in the body from invasion of a foreign agent which leads to specific immunity or hypersensitivity of the body to the foreign agent." He recalled the belief of von Pirquet (1907) that the rapid increase in size, between the eighth and twelfth days, of the areola surrounding the cutaneous papule of vaccinia represents a reaction in the tissues between the antibodies then being formed rapidly and the virus in the papule. This antigen-antibody reaction is occurring simultaneously in other parts of the body, as is evident from the sudden rise of temperature. Local and generalized exanthemata if they occur at all do so at about the time when this reaction is nearing its height. So too do the cerebral complications of vaccinia, in about 90 per cent. of cases. After revaccination the onset of encephalitis is said to be accelerated, as are similarly the cutaneous manifestations of vaccinia. In the case of other infections also, the incubation period of encephalitis is related to that of the particular exanthem with which it is associated. Whatever the preceding disease

the nervous lesions are identical. Finley regards them as resulting from an allergic response of the central nervous system to the virus of the exanthem.

Neurological complications, though not apparently a condition in any way resembling post-vaccinal encephalitis, may follow the exhibition of therapeutic sera (Kennedy, 1929; Allen, 1931; Doyle, 1933; Roger, Poursines and Recordier, 1934; Kraus and Chaney, 1937; and others). They are mostly of short duration, with signs pointing to involvement of the peripheral nervous system. In the cerebral type, due supposedly to intracranial or cerebral œdema, such disturbances of function as hemiplegia, aphasia, thalamic sensations, cerebellar seizures and amblyopia may be apparent. Kennedy (1936) described similar disturbances, often recurrent, in patients sensitive to particular articles of diet, &c. He considered that these manifestations of localized allergic œdemas resemble in many ways those of disseminated sclerosis. Baer and Sulzberger (1939), however, found no evidence of an allergic (atopic) mechanism at work in this disease.

If a relation exists between allergy or anaphylaxis and demyelination, it should be evident on experimental study. Few authors have investigated this field. Davidoff and his colleagues (1931*a* and *b*, 1932, 1934, 1935) produced local sensitivity of the brains of rabbits and dogs by various experimental procedures, most of which involved multiple intracerebral injections of antigen. Localizing nervous symptoms followed an intravenous or an intracerebral shocking dose of the antigen (horse-serum or egg-albumin). In the rabbit, lesions consisted in massive softening and hæmorrhage, œdema and leucocytic exudation. Alexander and Campbell (1937) obtained essentially similar results in guinea-pigs sensitized with a single intraperitoneal dose of serum and later injected intracerebrally with the antigen. They observed hæmorrhage, vascular thrombosis, necrosis, demineralization, leucocytic invasion, &c., and found the lesions only quantitatively more marked than those in control animals. Kopeloff *et al.* (1936) extended the observations to monkeys, in which animals anaphylaxis is less readily induced, with similar clinical results. Jervis *et al.* (1941) studied the histological changes so produced; it is perhaps unfortunate that these followed intracerebral injections of antigen often numbering several dozen and obviously introducing complicating factors which render difficult the interpretation of the results.

Jervis *et al.* described two types of lesions in the brains of their monkeys. In the local reaction at the site of deposition of antigen, widespread central necrosis was surrounded by a zone in which the myelin sheaths were chiefly involved; this lesion could be regarded as a typical Arthus

phenomenon. The second and more interesting type of reaction occurred at sites remote from this. Foci of demyelination, often surrounding a small vessel, and larger similar areas contained a variety of cellular elements, including granular corpuscles, lymphocytes, plasma-cells, polymorphonuclears and peculiar multinucleated giant-cells. These lesions resembled closely those observed by Rivers *et al.* and by Ferraro and Jervis after repeated intramuscular injection of heterologous brain and brain-extracts (*see above*). The general similarity of the lesions in the two groups of cases led Jervis *et al.* to conclude that in both the changes were due to the action of brain-specific antibodies. In the experiments at present under consideration, they supposed that these antibodies had arisen in response to an antigen consisting of foreign protein united to a specific haptene derived from the nervous tissue damaged by repeated intracerebral injection.

In a series of nearly 60 sheep and a few monkeys (unpublished experiments), I sought to produce allergic reactions in the brain without inflicting repeated injury upon the nervous tissues. In no case was simple demyelination a feature of the lesions.

The antigen used was egg-albumin in a dilution of 1:2 or pig-serum; it was administered intravenously twice or thrice weekly or intracisternally once weekly. Intravenous doses numbered from 5 in eleven days to 25 in ninety-five days. From the 10th day onwards, especially with egg-albumin, progressively more severe symptoms followed the doses; they included collapse, laboured breathing, escape of frothy mucus from the mouth, urination and voluminous fæcal evacuations. At times the mucus, urine and fæces were stained with blood. Several animals died within one to twenty-four hours of a dose of antigen; they showed no lesions in the central nervous system. To some sheep I gave, immediately after the antigen, intravenous pituitrin and adrenalin, in doses of about 1·5 c.c. per kilo. pituitrin (10 units) and 1·5 c.c. per kilo. 1:10,000 adrenalin;[1] the intention in so doing was to drive antigen through the blood-brain barrier and so to sensitize the brain without direct trauma. Intracisternal injections totalled from 3 in fourteen days to 13 in ninety-five days. Control animals thus treated showed in all parts of the cerebrum very heavy meningeal infiltration and perivascular cuffing with mononuclears. After a rest of a further nine to ten days the animals of both groups developed large wheals when injected intradermally with dilute antigen. The blood often contained precipitins, commonly to a titre of 1:40 or 1:60 but sometimes to one of 1:640 (egg-albumin) and once to one of 1:2,560. These titres, and the severity of the intradermal reactions, diminished considerably within three to four weeks. Preliminary treatment of the animals was now complete.

A week or so after the last intravenous dose of antigen, a few animals received from 3 to 5 doses of pituitrin and adrenalin in from two to three days in an attempt to force circulating antibodies through the blood-brain barrier. These animals were not those to whom similar treatment had been applied during immunization; subse-

[1] These doses are about twenty times those tolerated by the rabbit (Cooke, Hurst and Swan, 1942).

quently they received "mayonnaise" (*see below*). The majority of the intravenously inoculated animals were tested about eleven days or about five weeks after the last dose of antigen (*a*) by intracerebral injection of 1 c.c. of 1:2 antigen, or (*b*) by intracisternal injection of 5 c.c. of a similar dilution. Among the intracerebrally inoculated sheep I observed four cases of massive hæmorrhagic necrosis (Arthus phenomenon).

Near the actual site of inoculation a large central hæmorrhage was surrounded by a wide zone of necrosis of grey and white matter displaying many smaller hæmorrhages. Further away a number of smaller foci of necrosis existed without hæmorrhage. Occasionally such a focus was seen in the contralateral hemisphere; both here and on the inoculated side they occurred more frequently in the white matter than in the grey. The whole group of lesions was far more extensive and severe than anything caused in the non-sensitized animal by cautiously introducing 1 c.c. of the relatively bland fluid. At the junction of the continuous necrotic area with surrounding normal tissues necrosis was sometimes perivascular, with deposition of fibrin in the perivascular spaces and in the altered area outside the vessel wall. These areas stained a brighter orange than normal with van Gieson's stain (c.f. acute hæmorrhagic leucoencephalitis, Hurst, 1941*a*). In those cases in which, presumably, antigen had leaked into the subarachnoid space, the meninges were densely infiltrated with polymorphonuclears and mononuclears, many already necrotic and fading on the third day. The perivascular spaces throughout the cerebrum showed marked cuffing with mononuclears, as after repeated intracisternal inoculation of antigen. In no case was simple demyelination found at autopsy three to seven days after the test-injection.

The sheep sensitized by repeated intracisternal inoculation, and the small group of intravenously inoculated animals referred to above as treated with pituitrin and adrenalin after immunization, received antigen as a constituent of "mayonnaise" introduced into the cerebral capillaries (*see* Hurst and Cooke, 1942). The only demyelinating lesions found in these cases were those described previously in unsensitized sheep and due to minor obstruction in the capillary circulation of the cerebral white matter (Hurst and Cooke, 1943).

Jervis (1943) observed demyelination in the brain-stem of guinea-pigs in which Forssman antibodies were inoculated into one carotid artery. Forssman antigen is normally present in the tissues of the guinea-pig. After tying the artery distally the injection proceeded centripetally. Vital staining demonstrated subsequent greatly increased permeability of the hæmato-encephalic barrier over the homolateral medulla, pons and cerebellum. Animals surviving from five to ten days showed in these regions foci of demyelination which did not depend on vascular thrombosis or embolism. Subdural injection of the antibodies led to changes characteristic of the Arthus phenomenon. Jervis concluded that the areas of demyelination occurred at the site of an antigen-antibody reaction permitted by the permeability of the hæmato-encephalic barrier to circulating Forssman antibody.

In the belief that they were anaphylactic in origin, Dechaume and Croizat (1929), Garcin and Bertrand (1935) and Baginski *et al.* (1939) recorded various appearances in the brains of rabbits or guinea-pigs given

repeated parenteral injections of foreign serum without direct trauma to the brain. Demyelination did not appear to be a feature. Stief and Tokay (1934) in guinea-pigs, rabbits and dogs dying after anaphylactic shock found hæmorrhagic vascular and degenerative parenchymatous changes. The results of some other observers have been essentially negative.

It is clear that the effects of repeated inoculation of foreign nervous tissue, mentioned in the preceding section, and the rôle of antigen-antibody reactions in leading to demyelination merit further study. At the moment final conclusions do not appear to be warranted.

Demyelination in Virus Diseases of the Nervous System.

Demyelination has seldom been listed among the lesions produced by viruses infecting the nervous system. Again, viruses have not often been considered seriously as possible ætiological agents of the various demyelinating maladies. No experimental support is forthcoming for the belief that the post-vaccinal type of encephalomyelitis results from the direct action of the virus of whatever exanthem precedes it, or for the alternative view that the exanthematous infection wakens to activity a latent encephalitogenic virus. In the case of the nervous disease ("nervous distemper") following distemper in dogs, however, recent studies point to the distemper virus as the agent responsible for the demyelination.

In "nervous distemper" there may exist side by side lesions of the grey matter characteristic of attack by a neurotropic virus, and in the cerebellar white matter, brain-stem and elsewhere, demyelinating lesions closely resembling those found in some human diseases. The latter, first described adequately by Perdrau and Pugh (1930), are usually the more conspicuous. Clinically, the nervous manifestations of distemper ordinarily become apparent several weeks after the catarrhal symptoms of the disease, but they may develop without obvious initial illness. Perdrau and Pugh, therefore, doubted the direct causal relation of distemper to the disseminated encephalomyelitis in question, and regarded the latter as more nearly analogous to post-vaccinal encephalitis. On the other hand, Marinesco *et al.* (1933) described the condition as a "leuco-polionévraxite" intermediate between those conditions excited by viruses destroying mainly the grey matter (poliomyelitis, rabies, &c.) and the post-vaccinal type of encephalomyelitis which affects predominantly the white.

The experimental work of Hurst, Cooke and Melvin (1943) suggested that the cause of the demyelination in disseminated encephalomyelitis of dogs is the distemper virus itself. Inclusions similar to those formed

in infections with known distemper virus were often present in the lesions, and a virus indistinguishable from that of distemper was isolated from the brains of affected dogs. In the brains of animals inoculated intracerebrally and intramuscularly either with nervous material from cases of encephalomyelitis or with known distemper virus, there existed already at the time of onset of systemic symptoms of distemper early lesions characteristic of "nervous distemper." Apparently the affinity of the virus of canine distemper for certain parts of the white matter is more marked than that of most viruses affecting the nervous system. According to circumstances it may cause almost complete destruction of the white matter, which is then reduced to a mass of granular corpuscles, blood-vessels and collagen, or it may be responsible for demyelination accompanied or not by destruction of the axis-cylinders.

In a few other virus diseases the white matter is involved to a variable extent. Thus Perdrau (1936) described areas both of demyelination and of necrosis in the cortex and subcortical white matter of human cases of Australian X-disease. King (1938) recorded loss of myelin in equine encephalomyelitis; later (1939) he stated that "there is nothing selective about the process, and the myelin disappears only as a part of the general tissue disintegration. . . . There are many instances of myelitis and encephalomyelitis in man in which the observations are similar." Similar observations in equine encephalomyelitis were made by Branch and Farber (1939), Breslich, Rowe and Lehman (1939), Adler (1941), Baker and Noran (1942) and Weil and Breslich (1942).

In the foregoing instances demyelination is obviously the result of a direct attack of a virus upon the cells of the white matter. In the case of dog distemper the presence of nuclear inclusions in the glial cells is evidence of the presence or activity of the specific virus.

Biochemical Studies in the Demyelinating Diseases.

What we may term the chemical approach to the study of the demyelinating diseases has concerned (1) the myelolytic effect of plasma, serum or urine *in vitro* on the spinal cord of dogs or rats, and (2) the demonstration of various abnormal enzymes in the serum.

Weil (1930*a*, *b*, *c*) developed a technique of incubating at 37° C. pieces of animal cord with the material to be studied; thereafter he fixed and stained the preparations. Under these conditions he demonstrated that substances possessing a hæmolytic action (saponin, sodium taurocholate, cobra-venom and streptolysin) caused a broad zone of demyelination at the periphery of the cord. The myelolytic and hæmolytic properties of

the various substances did not run strictly parallel. The addition of cholesterin, lecithin, red blood corpuscles or suspensions of brain inhibited the action to a greater or less extent, depending on the substances combined and their relative concentrations.

Using Weil's technique, Brickner (1930) found that human plasma from cases of disseminated sclerosis was more myelolytic towards rat-cord than was that of controls. In later publications (1931, 1932, 1936) he maintained that abnormal enzymes acting on lecithin and other substrates existed in the serum. His figures were the outcome of grouped observations; they were not applicable to the diagnosis of individual cases of the disease. He did not claim that the abnormal activity was the pathogenetic factor in disseminated sclerosis, but he did believe (1936) that the activity of at least one enzyme rose during a remission of the disease and fell during periods of clinical activity.

Richards and Wolff (1940) criticized Brickner's chemical work on technical and other grounds. Estimating by a "more accurate" manometric method the esterase, lipase and choline-esterase in a number of diseases, they observed no difference in the behaviour of the serum from patients with disseminated sclerosis and of serum in other illnesses. In cases of the former, the activity of the enzymes did not vary with the clinical state of the patient. Swan and Myers (1937) also found no abnormal lipolytic activity of the serum in cases of disseminated sclerosis.

Crandall and Cherry (1931) detected an enzyme splitting olive-oil in the serum of 63 per cent. of 19 cases of disseminated sclerosis. Equally high figures obtained with disease of the liver or pancreas, but not in other conditions. High values for diastase both in cases of disseminated sclerosis and of hepatic disease suggested that the results in the former signified a functional abnormality of the liver.

Using the rat-cord technique, Weil and Crandall (1932) found that the sera of dogs subjected several days previously to ligation of the common bile-duct or pancreatic ducts contained a "neurotoxic" substance destroying both myelin sheaths and axis-cylinders. Furthermore, Crandall and Weil (1933) showed that dogs so treated may develop one or more of the following nervous lesions; (1) spongy necrosis of the nervous tissue; (2) active glial proliferation with the formation of large, round or oval nuclei; (3) diffuse changes in the nerve-cells especially marked in the deeper cortical layers and striate body—sometimes the striate bodies were symmetrically destroyed; and (4) extensive demyelination in the white matter of the hemispheres and around the vessels of the striatum. They noted that an abnormal lipase in the serum of their animals reached its maximum con-

centration before the "neurotoxic activity" appeared, and that this remained strong after the lipase disappeared. Moreover, as indicated by experiments with rat-cord *in vitro*, the lipase disappeared on heating the serum to 62° C., while the neurotoxic activity persisted.

Finally, although Weil and Cleveland (1932) confirmed Brickner's observation that serum from cases of disseminated sclerosis often acts destructively *in vitro* on the spinal cord of the rat, they found that the damage did not parallel the lipase content of the serum. They reinforced the suggestion of Crandall and Cherry (1931, 1932) that the increased lipase might be evidence of a lesion of the liver. A damaged liver might "eliminate" a myelolytic toxin or might "prepare the way for the passing of toxic metabolic products through the hemato-encephalic barrier." Hepatic lesions are known to occur in infectious diseases, metabolic disturbances and other conditions believed to favour the onset of disseminated sclerosis. Weil and Cleveland also could not exclude the possibility of primary nervous disease with upset of the nervous control of metabolism.

Weil (1931) showed that the concentrated urine from cases of disseminated sclerosis also caused demyelination in the spinal cord of the rat. This property is not confined to the urine of disseminated sclerosis (Weil, Luhan and Balser, 1935); it is more marked during periods of exacerbation of the disease (Weil and Heilbrunn, 1941).

Miscellaneous Observations on Demyelination.

Effect of tetanus toxin.—Following an early observation of Claude (1897) on a single dog, Putnam *et al.* (1930, 1931, 1932) recorded patches of perivascular demyelination with perivascular infiltration and gliosis in 2 of 80 dogs inoculated with small doses of tetanus toxin. Changes in the nerve-cells and axons were inconspicuous. In view of the facts summarized above in the section on nervous distemper, a positive result in so small a porportion of animals may suggest the need for caution in interpreting these findings. However, a very few writers (*see* Baker, 1942) have described demyelination following tetanus in man. Baker found perivascular changes in the myelin when symptoms of the disease had lasted for more than five to seven days. The extent of demyelination varied directly with the duration of the illness; it was greatest in the direct vicinity of the vessels affected. Perivascular necrosis also occurred, and in the more prolonged cases large, confluent areas of tissue destruction resulted.

Saponin and bee-venom.—Cornil *et al.* (1938) produced foci of demyelination in the lumbo-sacral cord and inferior and middle cere-

bellar peduncles of dogs in which saponin was injected into the subarachnoid space. Cornil *et al.* (1939) observed areas of demyelination in the white matter of the brain and spinal cord and in the peripheral nerves of mice and guinea-pigs injected subcutaneously with bee-venom.

Acute epizöotic leucoencephalitis of horses.—The lesions of this disease consist in bilateral softening almost wholly localized in the cerebral white matter (MacCallum and Buckley, 1901; Graham, 1936; Hurst, 1940). The situation and general character of the lesions, which develop within the course of a day or two, suggest that the condition is a very acute representative of the group of demyelinating maladies. Butler (1902) and Schwarte (1938) claim to have reproduced it by feeding mouldy, worm-eaten corn. Biester, Schwarte and Reddy (1940) failed to determine which of several moulds isolated was responsible.

Nutritional disorders.—I have made no attempt to review the demyelination occurring in various deficiency diseases, whether of vitamin or of essential minerals, since for the most part experimental work has led only to scattered degeneration of individual myelin sheaths quite different from the type of degeneration occurring in the demyelinating diseases of man. References to this work may be found in the articles of Findlay (1940) and of Innes and Shearer (1940). The observations of Brickner and Brill (1941) suggested a possible connection between nutritional inadequacy and disseminated sclerosis.

Summary

The foregoing summarizes much of our recent knowledge of demyelination as a morbid process rather than as a feature of the spontaneous demyelinating diseases of man and animals. The known antecedents of demyelination and the means by which it may be produced experimentally are very diverse, and appear to include no common determinant more narrowly specific than injury to the white matter of one type or other. We cannot fail to remark upon the frequency with which either (1) necrosis of tissue and demyelination are associated in one and the same case, or (2) necrosis replaces demyelination under a given set of experimental conditions as the intensity of the pathological process increases. In the field of human pathology we find recorded observations which may be interpreted as analogous, e.g. in hæmorrhagic encephalitis (Baker, 1935), acute hæmorrhagic leucoencephalitis (Hurst, 1941*a;* Henson and Russell, 1942), encephalomyelitis following therapy with arsenical pre-

parations (Russell, 1937) and disseminated sclerosis (Scheinker, 1943*c*).[1] As I have stated on several previous occasions, demyelination appears to be the response of the white matter to injuries short of those immediately lethal to the tissues. Although this conclusion is of little value to those concerned more directly with the ætiology of the spontaneous demyelinating diseases of man and animals, it does at least suggest that efforts to incriminate a single agent are likely to be unprofitable. It also suggests that the appearance of demyelination under purely experimental conditions does not necessarily furnish a clue to the ætiology of those human diseases of which the causation is at present obscure.

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[1] Recently I have seen a case in which a large but symptomless demyelinated plaque of many weeks' duration existed in the cerebellar white matter. Ten days or so before death the patient developed an acute ascending necrotic myelitis and died of pulmonary embolism. The lumbar cord was almost completely necrotic and was reduced to a mass of cuffed blood-vessels and granular corpuscles. In the mid-dorsal cord lesions were much more recent; they consisted in acute necrosis of the nervous tissues, which apart from scanty polymorphonuclear infiltration showed no cellular or vascular reaction. Accidental arrest, at a critical moment, of the progress of the nervous lesions allowed the pathologist to witness in one and the same case changes analogous to those encountered under various experimental conditions in poisoning with cyanide, &c.

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FIBRE INTERACTION IN INJURED OR COMPRESSED REGION OF NERVE.

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It has long been known in classical electrophysiology that severance of the nerve is a factor of significance for the excitability of the frog's nerve-muscle preparation. Thus Pflüger's (1859) observation that the upper end of the nerve is more excitable than the end towards the muscle was accounted for by Heidenhain (1861) by his finding that nerve excitability is increased in the region near a cross section. With modern methods Adrian (1930) showed that the excitability at the cut end of a nerve is sufficiently high to cause a spontaneous discharge of impulses, and Adrian as well as Skoglund (1941) demonstrated that cross sections of *sensory* nerves are far more efficient impulse generators than those of *motor* nerves.

But the most remarkable experiment in this field was published as long ago as in 1882 by Hering: he cut the sciatic plexus of a frog, tied a knot around the nerve at the knee and stimulated through a pair of electrodes just above the knot. Muscles *above* the knee were then found to contract, signifying that impulses caused by the stimuli had ascended the nerve fibres to the cut end of the plexus in the pelvis there to pass over into adjacent motor fibres innervating muscles above the knee region. Nerve fibre interaction thus may take place at an injured region which in this respect serves as an artificial synapse. Hering added that the experiment only succeeded with especially excitable preparations. Uexküll (1894) confirmed this effect and found that it disappeared when the cut end was shunted with a solution of 0·5 per cent. NaCl.

Since the possibility of fibre interaction in a pathologically altered region of a nerve is a question of considerable importance for clinical neurology (causalgia, sciatica and other neuralgic pains, referred pain) it is surprising how little attention has been devoted to experimentation in this field, and how commonly either central effects or fibre dichotomy are invoked to explain every apparent exception to the classical law of isolated conduction in nerve fibres. The experiments to be presented in this paper contain some new observations on fibre interaction in mammalian nerve which also emphasize clinical aspects of this problem.

If at this phase of the operation, stimulating electrodes are applied to the motor root of L7 and leads are taken to the oscillograph from the sensory root of L7, as in fig. 1 (the picture marked "Standard"), stimula-

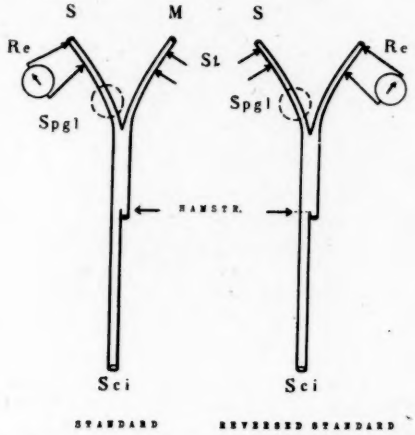

FIG. 1.—Diagram of placement of stimulating electrodes (St) and recording electrodes (Re) on Motor (M) or sensory (S) root, Sci, sciatic nerve; Spgl. spinal ganglion (*see* text).

tion of the motor root causes a volley of impulses to appear in the sensory root. It can be shown that this volley is a "back-response" from the gastrocnemius muscle (absent in the figure). Its latent period is so brief that the whole process is over long before the muscle has had time to contract and stimulate its stretch receptors. We noted this "back-pressure" here but soon found that it had been described before by Lloyd (1941) whose pictures are identical with our own. The "back-response" is due to electrical cross-stimulation in the muscle, probably at the region of the motor end plate.

From the point of view of this work this interesting back-response from the muscle is a source of error. Hence complete denervation of the limb must be carried out with the utmost care and the muscles around the hip joint and spine have to be cut at their insertions. When this has been done a preparation is obtained such as the one marked "Standard" in fig. 1. The severed ends of the hamstring and sciatic nerves are shown in the figure to emphasize that these are the important regions with which this paper will deal.

After complete denervation our "standard" experiment can be carried

The recent history of research in this field is relatively brief. It has been shown by Jasper and Monnier (1938), Arvanitaki (1940) and Katz and Schmitt (1939-40) that cross excitation between adjacent fibres can easily be demonstrated in crab nerves. In frog nerve this does not happen normally (Holzer, 1936) but if the excitability in a certain region of the nerve is increased by stimulation with a constant current (Otani, 1937), by dehydration, or by treatment with various hypertonic solutions (Kwassow and Naumenko, 1936) stimulation of some fibres induce activity in others. Similarly Rosenblueth (1941) has shown that after application of a constant current to any region of a cat's nerve the impulses carried by some fibres may stimulate other adjacent fibres. In an interesting paper Renshaw and Therman (1941) have modified Hering's original experiment and demonstrated that impulses passing up along the dorsal columns are reflected at a cross section in the spinal cord and thrown back into other column fibres so that they can be picked up from the dorsal roots.

Technique.

In this work nerve activity is recorded with an amplifier and a cathode ray oscillograph. The electrical stimulus to the nerve (1-2 per second) has been synchronized with the sweep circuit of the cathode ray so that each time the beam of the cathode ray passes horizontally across the face of the tube this movement starts at the moment of stimulation of the nerve. The impulse activity is pictured at right angles to the sweep movement so that the effect of the stimulus can be observed as a standing vertical wave on the horizontal abscissa written by the cathode ray. Thus, when the film slowly passes vertically across the beam of the oscillograph a series of successive pictures is obtained such as in fig. 2, illustrating the moment of stimulation to the left and the volley discharged into the amplifier after a latent period measurable in milliseconds somewhere in the middle of the picture. The time marking in the figures is always in milliseconds.

Cats have been used throughout as experimental animals. The details of the operation will be given below. The animals have been in a metal box the floor of which formed the bottom of a water-bath heated from the outside. A moist atmosphere and high temperature were thus secured.

Results.

(1) *The standard experiment. Some precautions. The effect of the anæsthetic.*

The best anæsthetic was found to be chloralose, a 1 per cent. solution, injected intravenously. About 5-6 c.c./kg. were given. Then the spinal cord was exposed, the dura opened, and the dorsal and ventral roots from L1 to S5 severed. Knots were tied around the ends of L6 and L7. In most cases the L7 pair of roots was used. The sciatic stem was exposed and branches severed up to the bony canal.

electrodes are on the motor root as in the standard experiment but the leads to the oscillograph have been shifted down the nerve as shown in fig. 3. The electrical shock to the motor root will then elicit a typical direct diphasic wave (fig. 4 *a*) at the leads. In the figure this is the first

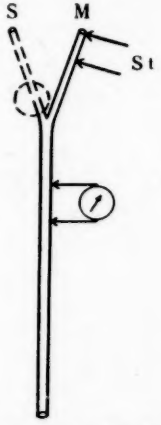

FIG. 3.—Recording galvanometer (oscillograph) placed on the sciatic nerve, stimulating electrodes on the motor L7, as described in text.

FIG. 4.—Records taken with stimuli and leads as in fig. 3. Record *a*, first follows "direct wave" from motor root; after vertical line, wave with opposite phase leading and hence reflected from end of nerve. In *b* stimulus for "direct wave" weakened. Reflected wave generally augmented by cutting end of nerve.

wave that begins with an upward swing, signifying that the travelling volley has reached the upper lead in fig. 3. It is followed by the well-known change of sign with a smaller swing in the downward direction when the wave of activity passes the lower lead on the nerve. This first and direct diphasic wave in fig. 4 *a* is followed by a small wave (after 2 msec.) travelling in the *opposite* direction. This conclusion can be drawn from the fact that the first phase of the second diphasic wave is a *downward* swing of the oscillograph, and the second smaller phase an upward move-

out. The motor root of L7 is again stimulated. The leads on the sensory root (fig. 1) then record a discharge such as the one illustrated in fig. 2 *a*

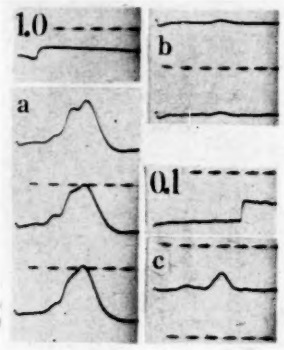

FIG. 2.—Above *a*, calibration to 1·0 mV. Time in this and all records to follow in msec. *a*, response to stimulation of motor L7 picked up in sensory L7 (standard); *b*, reversed standard (*see* text). 0·1 calibration to 0·1 mV; *c*, reversed standard.

in three consecutive pictures cut out from a long series. The slight variations seen are characteristic. The calibration to 1·0 mV. above the picture shows that the volley is of a large order of magnitude. Somewhere in the nerve the volley of impulses set up in the motor fibres at the root have been transmitted to the sensory fibres and thus have become measurable at the sensory root. In the next row (*b*) the stimulus has been shifted to the sensory root and the leads to the motor root. We shall refer to this arrangement (fig. 1) as "Reversed standard." The two consecutive uppermost records of the series show a very small hump on the baseline. We therefore increase amplification so that calibration to 0·1 mV. (above *c*) now gives a deflection about twice the size of the deflection to the ten times larger voltage used for series *a*. The lowermost picture *c* then shows that a volley of somewhat less than 0·1 mV. can be seen in the motor root upon stimulation of the sensory root. In many, if not in most cases, nothing whatever can be observed in the reversed standard when large volleys are noted in the standard combination. In general, therefore, there is far more resistance to transmission by fibre interaction in the direction sensory —→ motor, than in the direction motor —→ sensory.

Where does the fibre interaction take place? There are several methods available for answering this question but one of the most direct ones is used in the experiments illustrated in figs. 3 and 4. The stimulating

ment. Hence in this case the *lower* lead on the nerve has been influenced before the upper one. The second wave in fig. 4 *a* is therefore relayed somewhere from the end of the cut sciatic nerve. In this region it must have been transmitted from motor fibres into sensory fibres by fibre interaction. The long interval between the first and the second wave place this region at the cross section of the sciatic nerve. (Fig. 4 *b* showing a much larger second or relayed wave will be discussed below.)

In the type of experiment presented in figs. 3 and 4, with leads on the nerve below the hamstring level, the evidence conclusively points to the cut end of the *sciatic* being the region where the volley to the motor fibres is transmitted into the sensory fibres. But in the standard experiment with leads on the sensory root it has turned out that the cut end of the hamstring or some nerve severed above this level also is an exceedingly active region of transmission. In most cases the relayed response consists of two volleys as in fig. 5. Sometimes they are separated from each

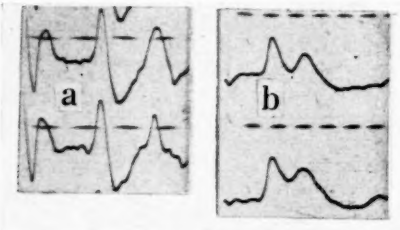

FIG. 5.—"Standard" arrangement of fig. 1. Record *a* begins with unusually large shock artefact from stimulus. Explanation in text.

other by a definite interval, as in 5 *a*, sometimes, and more generally, the response is expanded and contains two separate peaks, as in 5 *b*. By measuring both the latent periods of the two relayed waves as well as the actual impulse velocities it is possible to separate the hamstring cross-section from the sciatic cross-section as source of relayed volleys. In the standard combination the latent period of the response relayed from the cut end of the hamstring nerve is of an order of 1·8 msec., whereas it lasts about 3 msec. before a volley from the motor root can be picked up from the sensory root if cross-excitation has taken place at the cut end of the sciatic nerve in the knee region. By making a fresh section of the nerve in the regions concerned it is often possible to find out whether the "artificial synapse" was localized to the one or the other nerve cross-section. This question will be taken up below.

The experiments have thus shown that fibre interaction is a normal process at an injured region of a mammalian nerve. Hering saw this happen only in the plexus ischiadicus of hyperexcitable frogs. Our results have added the theoretically and practically significant fact that impulses with much greater ease are transmitted in the direction motor ——→ sensory (our standard combination) than in the reversed direction. This "artificial synapse" at the cut end of the nerve behaves like other synapses in that it is very sensitive to the anæsthetic. Some decerebrate animals were used in order to study fibre interaction without complications of this nature. The standard experiment was successful in all these cases. Dial was tried and found to be unsatisfactory. Sometimes the effect was present, sometimes absent. But decerebrate and chloralosed animals are both extremely reliable preparations, provided that the cat is in good condition. If the cat is asphyctic or too heavily narcotized fibre interaction disappears before the nerve ceases to transmit impulses.

(2) *The immediate effects of cutting or crushing a nerve.*

We return to the combination illustrated in fig. 3 in which (fig. 4 *a*) a direct diphasic wave is followed by a relayed wave starting with the opposite phase leading. The direct wave of fig. 4 *a* is next diminished by diminishing stimulus strength, as in fig. 4 *b*, but immediately afterwards the end of the sciatic is cut through with a pair of scissors. There is now in 4 *b* a very large increase of the second diphasic wave relayed from the freshly established cut, meaning that the number of fibres, involved in cross-excitation from motor to sensory fibres, has risen in a very considerable manner owing to the renewal of the injury.

The same experiment is repeated in fig. 6, but this time in the standard combination of fig. 1. In fig. 6 *a* is shown the relayed response transmitted

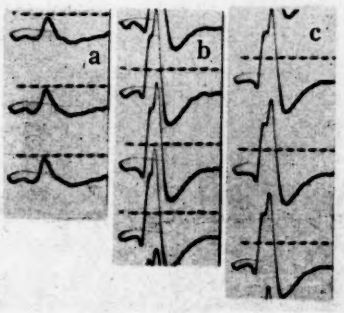

FIG. 6.—"Standard" arrangement, *a*, before, *b* and *c* after fresh section of nerve.

so large as to fall outside the picture. In order to show that the first phase of this large wave actually is relayed from the hamstring and not from the sciatic the hamstring is freed and a knot is tied around it 1 cm. higher up. This shifts the transmitting region further up by the same amount. The effect is shown in *f*. The first phase of the wave is now again better set off from the rest of the response and, besides, has increased in magnitude.

It is concluded from this experiment that a crushed region obtained by tying a knot around the nerve, is equally effective as a cross section in setting up an artificial synapse and that in both cases transmission in the direction motor —→ sensory undergoes a very considerable transitory facilitation by cutting or crushing the nerve in a fresh place. This effect is not always seen at the extreme end of the nerve where sometimes a fresh cut may cause a diminution of the relayed wave or no effect whatever but it is well marked in the proximal region. In experiments of the type illustrated above the facilitating effect of a fresh cut affords the best means of localizing the origin of a relayed wave. (Exceptions will be described below.) It is of practical significance that this facilitation is of a very large order and sometimes must involve most if not all fibres of a nerve. The facilitation diminishes with time, first rapidly, then slowly along an asymptote which cannot be followed for a sufficiently long period in acute experiments (with a nerve kept in good condition).

In order to study the relayed waves in the "reversed standard" which are very much smaller than in the "standard" arrangement it is convenient to utilize the facilitation caused by a fresh section. In fig. 8 *a* a loose knot

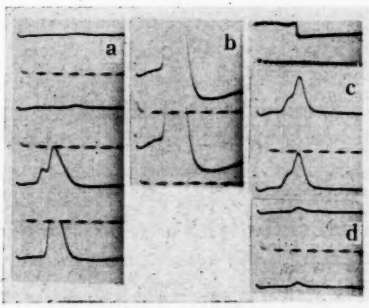

FIG. 8.—Fully explained in text.

has been passed round the end of the nerve, set up in the "reversed standard" arrangement. The two first records show that the relayed

in the direction motor ——→ sensory some time after the nerves had been severed. The main sciatic stem is then cut across with a sharp pair of scissors. The increase of the relayed wave, that follows in 6 *b*, by 4 times exceeds the control. The records 6 *c* are taken about a minute later. The amplification or "facilitation" of transmission at the "artificial synapse" by a fresh cut lasts from five to ten minutes or more. The duration of this period varies a great deal from animal to animal. Cross-sections at the upper portion of the nerve tend to give far more facilitation than those at the lower portion.

In the next experiment we are using the standard arrangement and proceed to tie a series of knots around the sciatic nerve beginning just at the end. Fig. 7 shows in *a* the control, a relayed volley with two peaks, the

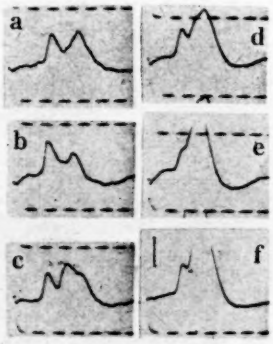

FIG. 7.—"Standard" arrangement. Records fully explained in text. Calibration to 1·0 mV. marked in record *f*.

first coming from the cut end of the hamstring, the second from the end of the sciatic. In *b* the second peak (sciatic) diminishes somewhat when a loose knot with a thread at the end of the nerve is tightened. The same procedure is repeated 1 cm. up the nerve in *c*. Now the wave relayed from the crushed region definitely increases. A fresh knot is made 1 cm. further up, and in *d* a large increase of the wave relayed from this knot is seen to occur. Finally the nerve is tied still higher up in *e*. This last knot on the main sciatic stem is now so near the reflecting region at the cut end of the hamstring that the first wave from the latter merely is indicated as a hump on the rising phase of the wave relayed from the crushed region under the knot on the sciatic. The relayed response is now

which, according to the biological test applied is of a relatively moderate order of magnitude.

In order to present a case which as nearly as possible imitates selective pressure on sensory fibres of the sciatic nerve the effect of compression will here, in fig. 9, be illustrated with the aid of the less usual combination

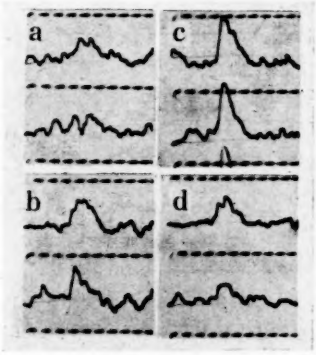

FIG. 9.—Fully explained in text.

sensory ⟶ sensory. The sensory root S1 of an apparently post-fixed cat was stimulated and the leads were on the sensory root L7. It is a convenient arrangement also because the relayed response from the cut end of the sciatic is of a moderate order though somewhat variable, as shown by *a* in fig. 9. Then the lever is dropped and a weight of 60 gr. applied to the nerve by the lever. Fig. 9 *b* shows the effect on the relayed wave immediately afterwards; 9 *c*, after one minute. The volley sweeping through the compressed region has doubled in size. Finally the lever is removed, the nerve washed with warm Ringer, and eight minutes later the record 9 *d* is taken, showing that the facilitating effect of the compression has passed over, and that the relayed response again is of the same order as in 9 *a*.

Such experiments do not always succeed but from time to time positive results are obtained showing that fibre interaction *can* be caused by moderate pressure in sufficiently excitable nerves.

(4) *The length of the facilitating interaction. Distance effects.*

Hitherto the facilitation has been described as an effect localized exclusively to the cut or crushed region. In a number of experiments,

response originally is very small. Between the second and the third record the knot is quickly tightened with the result that the relayed response immediately undergoes a very great amplification. Already in the second response a second later (the fourth in record *a*) the relayed response has reached its maximum and the beam of the cathode ray is thrown just out of focus. In *b* this effect is compared with the "standard," taken immediately afterwards. In the standard arrangement the relayed response is a great deal larger. Finally, in *c*, the sensitivity is decreased (calibration to 10 mV.) and the standard (*c*) is quantitatively compared with the reversed standard *d*. The relayed response in the standard combination is of the order of 25 mV., a truly impressive effect, as against the more than ten times smaller response in the reversed standard. Fibre interaction may thus under favourable conditions mobilize practically the whole sensory input of a large nerve such as the sciatic. Facilitation disappears at a very much faster rate in the "reversed standard" than in the "standard" arrangement.

(3) *Compression without loss of conductivity.*

For fibre interaction it is not necessary to cut the nerve or crush it till it has lost its capacity to conduct impulses through the damaged region. Some experiments, designed to imitate pressure by the pulp of a vertebral disc on the roots in sciatica, were carried out in which the nerve itself was pressed against a plate of ebonite by an ebonite edge of 1 mm. operated by a lever. Pressures between 50-100 gr. were used but their actual values are of less importance because the biologically significant factor is conductivity under the compressed region and not pressure as such, and conductivity was measured directly. To this end stimulating electrodes were placed in the distal region of the cut sciatic, the leads in the usual manner being on the sensory root. The weighted lever was placed somewhere in the middle of the nerve between stimulus and leads. A submaximal volley is first sent from the stimulating electrodes at the end of the nerve to the leads at the root. Let the size of this volley in an actual experiment be 18 mm. Then the lever is weighted with 50 grm. The volley from the end of the nerve is reduced by this pressure to 12 mm. Finally the lever is removed, the nerve treated with warm Ringer solution and after a brief while it is found to let through the full 18 mm. volley again. With pressures up to 110 gr. there is a larger reduction of the direct volley but this volley can still be greatly augmented by slightly increasing stimulus strength, and the nerve shows full recovery after removal of the lever. We are thus concerned with reversible effects of a compression

Discussion.

In this work we have selected a number of facts from our experiments on fibre interaction at injured or compressed regions of nerve which describe some of the fundamental features of this process of transmission, those, namely, that would seem to be of interest to the clinical neurologist. Two of us have completed the work with an extended analysis of impulse. transmission at the artificial synapse from the points of view of theoretical neurophysiology. The facts selected for the present work do not therefore represent everything that at the moment could be said about this phenomenon. Those interested in following other aspects of the work are referred to a paper in course of publication (Granit and Skoglund, 1944).

The clinical aspects are so obvious that little need be said about them: an injured or compressed region forms a critical point at which impulses can be reflected centrifugally or centripetally by engaging other fibres by interaction, in particular sensory ones. Similar processes will occur in centres too. With these facts uppermost in mind the neurologist may be able to localize critical points of this character by observing what regions of the body are engaged in anomalous reactions.

But why, in particular, are the sensory fibres so easily engaged by interaction? The explanation of this fact probably lies in Skoglund's (1942) demonstration with cats that sensory fibres have lower threshold and far less accommodation than motor nerves. At any rate this explanation must be given serious consideration.

Accommodation may be defined as the resistance a nerve puts up to stimulation. If the accommodative resistance is low the nerve easily responds, even to slowly rising stimuli, if high, the nerve only responds to currents rising at a very fast rate. Fig. 11 from Skoglund's work illus-

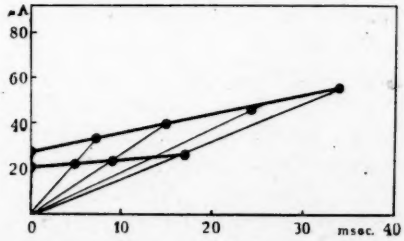

Fig. 11.—"Accommodation curves" for motor (upper) and sensory nerves (lower) of cat. Ordinates, stimulus strength in microamp., abscissae, stimulus duration in milliseconds. The linearly rising stimuli drawn in the figure. (From Skoglund, *Acta. physiol., Scand.*, 1942, **4**, Suppl. 12.)

such as, for instance, the one illustrated in fig. 4, this localization has also been experimentally verified. In such cases the "artificial synapse" must cover a relatively short stretch of nerve. But there is a large number of experiments in which cutting or crushing the sciatic facilitates the relayed response from the end of the hamstring and *vice versa*. This means that in suitable preparations a distance effect can amount to 3-4 cm., maximally perhaps up to 6 cm. In some cases the effect of the one nerve upon the other is a reduction of the relayed response instead of an increase. Why this should be so is not yet understood.

In order to throw some light upon this particular aspect of the general problem of fibre interaction an experiment of the type illustrated in fig. 10

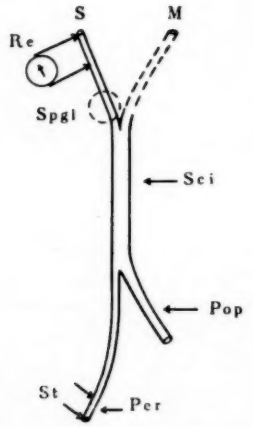

FIG. 10.—St, stimulating electrodes on peroneal nerve, Re, recording electrodes on sensory root.

was set up. The stimulating electrodes are on the peroneal branch (Per) of the sciatic which has been dissected free from the popliteal branch (Pop), the leads, in the usual manner, being on the sensory root. The experimental problem is simply: How does cutting or crushing the popliteal branch affect a volley set up electrically in the peroneal branch of the sciatic? In most cases it was found that cutting the popliteal with a pair of scissors augmented the response started at the end of the peroneal nerve. There were, however, some cases in which the effect was a diminution instead of an augmentation.

berg's (1944) work on accommodation in man the nerves were found to loose their accommodation a great deal easier in the upper region of the arm than in the lower region in experiments on hyperventilation and compression with pneumatic cuffs, and that spontaneous activity leading to positive Trousseau sign, fasciculations, etc., then started in the same region.

Summary.

In experiments on cats it is shown that nerve impulses, set up in a motor root are transmitted to the sensory fibres in a cut region of the nerve and can be picked up in the sensory root of the same segment. The cut region thus serves as an "artificial synapse."

Fibre interaction of this character also takes place at a crushed region, for instance, when a knot is tightened around a nerve somewhere along its course.

Fibre interaction is also described in a region subjected to mechanical pressure of a moderate order.

The transmission in the damaged region is of a much smaller order, if present at all, if the discharge is forced in the reversed direction, i.e. from sensory to motor fibres.

The effect is greatly facilitated in a freshly damaged region where most if not all sensory fibres can be excited to discharge by a volley passing them in motor fibres.

The fibre-fibre interaction is impeded by deep narcosis or general deterioration of the preparation.

The significance of this process for certain neuralgic symptoms, referred pain, causalgia, etc. is pointed out.

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trates the differences in accommodation between motor and sensory nerves. On the abscissa is found the time during which the linearly increasing stimuli to a nerve rise, on the ordinate the strength to which at any particular moment, given by the abscissa, the stimulus has risen. The linearly rising stimuli to the nerve (cat) are also inserted in the figure. This shows that it has been necessary to compensate decreased rate of rise of the stimulus by increasing current strength. The lower curve, referring to sensory nerves, shows that the rate of rise of the stimulus is of much less significance there than for motor nerves (upper curve). These "accommodation curves" express an important aspect of what is generally called "excitability." The absolute threshold or rheobase is also seen to be lower for sensory than for motor nerves as shown by the difference in initial values. The motor nerve thus has both higher rheobase and in addition accommodates or puts up resistance to stimulation, so that the slower the rise of the stimulus the more compensation necessary to overcome accommodation. The sensory nerves have this capacity to resist stimulation far less developed.

The lower rheobase and accommodation of the sensory nerves suggest a natural explanation of the directional properties of the artificial synapse at the cut end of a nerve. Recently Kugelberg (1944) has completed an extensive analysis of accommodation in man under various conditions and for motor and sensory nerves found differences identical with those in cats. As the small pain fibres of the so-called C-group apparently are practically lacking in accommodation (Grundfest, 1940) it is natural to expect them to be easily excited by fibre interaction. Some symptoms of causalgia would thus receive a very simple explanation on the basis of this view.

Cross-stimulation in the direction sensory ——→ sensory has been demonstrated by Renshaw and Therman (1941) at a cut surface in the spinal cord, as mentioned above, and even seems to occur without destruction of a path or a centre if accommodation has been diminished in the spinal cord, e.g. by cooling the cord. An instance of this is the so-called "dorsal root reflex," first described by Barron and Matthews (1935, 1938), then further elucidated by Tönnies (1938, 1939) and from the point of view of accommodation by Barron and Matthews (1938 *b*) and by Skoglund and Uvnäs (1943).

It was repeatedly noted that the effect of cutting or crushing a nerve was far more pronounced in the proximal than in the distal region of the nerve. This may have been due to better circulation further up the nerve but, on the other hand, it deserves to be pointed out that in Kugel-

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